ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF MENTAL HEALTH

FISCAL YEAR 1971
PARTS I-II

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PARTS I-II

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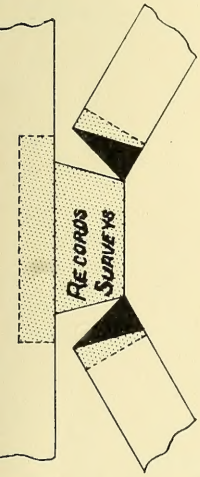

PART I

PART II

TABBED SEPARATOR SHEET
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ANNUAL REPORT

MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM - Division of Clinical and Behavioral Research, and Division of Biological and Biochemical Research

NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1970 - June 30, 1971

VOLUME I

Summary Statements

ANNUAL REPORT
MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM -
Division of Clinical and Behavioral Research, and
Division of Biological and Biochemical Research
NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1970 - June 30, 1971

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ANNUAL REPORT
of the
DIRECTOR, MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM
NATIONAL INSTITUTE OF MENTAL HEALTH
July 1, 1970 - June 30, 1971

John C. Eberhart, Ph.D.

The outstanding event of the past year in the NIMH Intramural Research Program was the award of the Nobel Prize in Physiology or Medicine to Dr. Julius Axelrod, Chief of the Section on Pharmacology of the Laboratory of Clinical Science. Sharing the prize with Dr. Axelrod were Sir Bernard Katz and Professor Ulf von Euler. The prize was awarded Dr. Axelrod "For discoveries concerning the storage, release, and inactivation of neurotransmitters from nerve terminals." The award was deeply gratifying to all his friends and colleagues, who gathered in the Clinical Center Auditorium on November 3, 1970, to do him honor.

Dr. Cohen and Dr. Salmoiraghi have reported on other honors and awards presented this year to Intramural scientists. It is an impressive list. Despite the limitations imposed by a decreasing staff and budget, the level of scientific work has continued remarkably high, as the summaries by Laboratory and Branch Chiefs make clear. I will not further summarize those research programs here, but instead would like to report on some other matters of interest.

On Friday, May 28, 1971, many members of the NIMH Intramural Research Program and their guests spent the day at the NIH Animal Center near Poolesville, Maryland, dedicating two new research buildings and a new Laboratory. It is fitting to give some details of that celebration, because it marks the completion of an effort that began 13 years ago in 1958.

At that time Dr. Paul D. MacLean, newly arrived (in 1957) Chief of the Section on Limbic Integration and Behavior of the Laboratory of Neurophysiology, and Dr. Robert B. Livingston, Director of Basic Research for NIMH and NINDB, proposed that a site be secured which would permit the study of animal behavior under quasi-natural conditions. Dr. John B. Calhoun, who was then actively at work in a remodeled barn in Rockville, joined in the proposal. As a result of their efforts, the NIH agreed to set aside approximately 40 acres of the newly acquired 500 acre Animal Center for studies of brain and behavior. Then began a process of planning, seeking funds, and construction, which lasted much too long and at times seemed interminable. Happily it has ended, and the two resulting buildings are attractive and substantial, and now dedicated to research.

The dedicatory address was to have been given by Dr. Roger O. Egeberg, Assistant Secretary for Health and Scientific Affairs, but he was unable to be present. Dr. Bertram S. Brown, Director of NIMH, graciously expanded his role on short notice and officially launched the new facility. Dr. Robert Berliner represented and spoke for the NIH, and Dr. MacLean

described the program of the new Laboratory for the 200 or so guests who attended the morning ceremony in the green and white striped tent. It was a pleasure to be able to introduce Dr. Robert Livingston, who flew in from San Diego to participate in the festivities. After a tour of the two new buildings, and of the temporary structure housing Dr. Calhoun's research, and a sandwich luncheon catered by the Sunshine Class of the Poolesville Memorial United Methodist Church, some guests returned to Bethesda, but about a hundred remained for the afternoon scientific sessions organized by Dr. MacLean and the members of his Laboratory.

Participants in the scientific sessions included Drs. Paul MacLean, Walter Stanley, and John Calhoun from the Laboratory; Dr. Frederick Snyder, Chief of the Laboratory of Clinical Psychobiology, and the following guests: Professor Byron A. Campbell of Princeton; Dr. William Jurgelsky of NIEHS; Professor Peter H. Klopfer of Duke; Dr. Livingston of the University of California (San Diego); Dr. Francis S.L. Williamson, Director of the Smithsonian Consortium; and Drs. Alan Beck, Stephen J. Rothstein, Wolfgang Schleidt, William Sladen, and Penelope Williamson from the Smithsonian Consortium.

It has seemed somehow a ceremonial year, with more than the usual opportunities for nostalgia. It may be a sign of program age, though the years hardly justify more than an adolescence. The first celebration of the year was of course the ceremony in honor of the award of the Nobel Prize to Dr. Axelrod. It included the directors of the NIMH, HSMHA, and NIH, and was, for all concerned, a moving tribute to a great scientist.

On Saturday, May 8, 1971, the friends of Dr. David Shakow organized an all day symposium in honor of his 70th birthday. The Clinical Center Auditorium was well-filled as Dr. David Rosenthal welcomed the guests and introduced Professor Norman Garmezy who presided with wit and feeling. Participating as authors of papers or as discussants were Drs. Joseph M. Bobbitt, Seymour S. Kety, Gardner Murphy, Leslie Phillips, Harriet L. Rheingold, Eliot H. Rodnick, Saul Rosenzweig, and Lyman C. Wynne. David Shakow closed the symposium with an account of major influences on his career.

Then followed the dedication of the new Laboratory of Brain Evolution and Behavior, with Paul MacLean as Chief, and yet to come is the June 28-29 celebration of the 25th Anniversary of the passage of the National Mental Health Act. A number of members of the Intramural staff will take part in that two-day look both backward and forward.

And in between have come ceremonies for more than the usual number of senior staff members who have retired after many years of service. The major loss to the Intramural Program was the retirement in July 1970, of Dr. Wade H. Marshall as Chief of the Laboratory of Neurophysiology. Dr. Marshall was the oldest Intramural scientist in point of service, and was one of the first Lab Chiefs appointed. His distinguished career honored the NIMH, and his scientific leadership resulted in much fine research from the members of his Laboratory over a twenty-year span. His colleagues, former students, and friends in neurophysiology have brought

together a series of papers in his honor which are being published in two or three issues of the International Journal of Neuroscience.

To succeed Dr. Marshall as Laboratory Chief, we invited Dr. Edward V. Evarts, Chief of the Section on Physiology of the Laboratory of Clinical Science, and we were very pleased that he was willing to accept this heavier responsibility. He is an outstanding scientist and has shown in earlier service as Chief of the Laboratory of Clinical Science an uncommon talent for management of a laboratory.

We were pleased to welcome Mr. John Land in May 1971 as Administrative Officer for the Division of Clinical and Behavioral Research. He came to us from the National Library of Medicine, succeeding Mr. Theodore Roumel, who left us in January.

The year just passed has been a repetition of the previous 3 years insofar as level of support is concerned. The Fiscal 1971 budget was about the same as in 1970--level for dollars and for positions. With the constant rise in salaries and in other costs of doing research, our program had to be operated on less. Some of the consequences of decreasing support on program were outlined in this space last year. There has been no marked change since then, though more of our time has gone into consideration of priorities for research support. We did not schedule another Lab Chief "retreat" as a followup to the all day discussion on April 30, 1970, but are considering a longer session for the fall of 1971. This spring we did have the opportunity to include Dr. Bert Brown in two Lab Chiefs' meetings for discussion of the future of the Intramural Research Program. They were helpful introductions to a large topic. More remains to be discussed and thought through, and further meetings will be held in the fall.

This summary of the year would not be complete without some comment on the development of an Equal Employment Opportunity Program within the Intramural Research Program. During Fiscal 1970, a committee of 12 IRP staff, under the chairmanship of Dr. Donald Boomer, Deputy EEO Officer, worked diligently to draft an "affirmative action plan" for the NIMH IRP. Their proposal was adopted with slight modification on May 1, 1970. It has since guided our EEO activities. The first implementing step was creation of an EEO Council by election and appointment. Elected as Coordinator (Chairman) of the Council was Mr. Garrett A. Bagley, of what is now the Laboratory of Brain Evolution and Behavior. On July 1, 1970, Dr. Boomer was succeeded as Deputy Equal Employment Opportunity Officer by Dr. Winfield Scott, of the Adult Psychiatry Branch. To both of these scientists we are indebted for their major contributions to the development of an effective Intramural EEO program.

An important contribution has been made by the EEO Counselors, who have spent many hours in meetings and working with individual staff members. Serving as Counselors have been Mrs. Arliene M. Aikens, Mr. James Boone, Mr. Nathaniel E. Singletary, and Mr. Terry B. Thomas. Other members of the EEO Council this year have been Miss Marlene Blauer, Mr. Ernest Gabriel, Mr. John Gordon, Mr. Richard Lehne, Mr. Leo Leitner, Mrs. Virginia Marbley, Dr. Leonard I. Pearlin, Mr. Theodore J. Roumel, Mr. Marvin Watkins, and

Dr. John Zinner. Dr. Marian R. Yarrow has served on the Council as Coordinator for the Federal Women's Program.

Some progress has been made during the year in the hiring of members of minority groups; in the provision of better information about training and promotion opportunities; in the start of a counseling service; and in improved acquaintance of administrators and Lab Chiefs on the one hand, with supporting staff and minority staff members on the other. Two joint meetings of Lab Chiefs and EEO Council were held, and two series of group meetings, each lasting two weeks, were held during May for minority staff, administrators, and EEO Council members, under the leadership of Dr. Pierre Turquet of the Tavistock Institute. More remains to be done, but a good start has been made.

It is a pleasure to report that in recognition of their contributions to the EEO program, the Surgeon General awarded Dr. Boomer the Commissioned Corps Commendation Medal for his outstanding leadership, and the Administrator of HSMHA awarded Mr. Singletary the Superior Service Award for his tireless and effective contributions.

No member of the Intramural Program was on a foreign work assignment during the year. The NIMH quota for such assignments was apparently one, and it was not awarded to either of our nominees.

The Board of Scientific Counselors met twice during the year. On October 30 and 31, 1970, the Board heard a review of the neuropsychological research of Drs. Rosvold, Mishkin, Goldman, and Semmes, plus the psychophysiological studies of Drs. Carlson, Buchsbaum, and Zahn. Present for that meeting were all four members of the Board: Dr. Douglas Bond, Chairman, and Drs. Melvin Calvin, Theodore Ruch, and Richard Solomon. At the spring meeting, on March 26-27, 1971, only Drs. Bond and Solomon were able to be present for reviews by Dr. David Shakow and Dr. Lyman Wynne of their respective research on schizophrenia; by Drs. Donald Boomer and Allen Dittmann of their work on communication; and by Drs. Albert Caron and Jacob Gewirtz on aspects of child development. During the executive session at this meeting, there was opportunity to discuss earlier suggestions that the traditional pattern of Board meetings be modified by reducing the number of full meetings to one per year, with each Board member making a second visit at his convenience to review the work of a laboratory he was especially interested in. After a rather thorough review of the proposal it appeared that neither Board members nor staff really wanted to eliminate one of the two annual meetings, and that involving Board members (and Lab Chiefs) in reviews of research that is at times outside their primary fields of interest or competence is not necessarily a bad thing.

In addition to the honors mentioned above, it is a pleasure to report the award of the Department's Superior Service Award on May 28, 1971, to Dr. William E. Bunney, Jr., Chief of the Section on Psychiatry of the Laboratory of Clinical Science; to Mr. William T. Burriss, Biological Laboratory Technician in the Laboratory of Neurophysiology; to Dr. Harold A. Greenberg, Chief of Clinical Care in the Division of Clinical and Behavioral Research; and to Dr. Marian W. Kies, Chief of the Section on Myelin Chemistry

of the Laboratory of Cerebral Metabolism. Dr. Paul D. MacLean, Chief of the Laboratory of Brain Evolution and Behavior, received the special research award from the American Psychopathological Association in February 1971 in recognition of his contribution to the field of brain function and sexual behavior. Dr. Richard J. Wyatt of the Laboratory of Clinical Psychopharmacology won the A. E. Bennett Clinical Science Research Award, and Drs. Floyd Bloom, Barry Hoffer, and George Siggins of the Laboratory of Neuropharmacology won the A. E. Bennett Basic Science Research Award, both from the Society for Biological Psychiatry in May 1971. To all of them and to the many others who have done distinguished work this year, I would like to extend my own congratulations and the gratitude of the NIMH. It may be fitting to close almost as I began, by reporting with pleasure the election of Dr. Axelrod to the National Academy of Sciences at the end of the year.

Annual Report of the
Director, Division of Clinical and Behavioral Research
National Institute of Mental Health

July 1, 1970 - June 30, 1971

Robert A. Cohen, M.D., Ph.D.

As I write this report we are approaching the 25th anniversary of the signing of the National Mental Health Act and the 18th anniversary of the opening of the Clinical Center which marked the actual beginning of intramural research operations. As a class, research administrators tend to live at least several years in the future, and may therefore find themselves speaking with two tongues. Looking forward I cannot avoid some Cassandra-like foreboding; looking back one cannot help but feel considerable satisfaction both in the scientific achievements of this program and in the professional development of so many former and present colleagues who are leading figures in the field today.

Honors continue to be bestowed on members of the staff. By far the most notable, of course, was the award of the Nobel Prize for Medicine or Physiology to Dr. Julius Axelrod--a distinction which requires no further embroidery with words of respect and praise. Dr. David Rosenthal won the Stanley R. Dean award for research in schizophrenia, the third time in its nine-year history that this prize was given to a member of our staff. Drs. William Bunney, Frederick Goodwin and Dennis Murphy were joint winners with Joseph Schildkraut, now of Harvard Medical School but formerly of our staff, of the Hofheimer Prize awarded by the American Psychiatric Association. Dr. David Shakow added to his long list of awards an honorary degree from the University of Rochester and the Salmon Medal for outstanding contributions to psychiatry to be presented by the New York Academy of Medicine. Dr. Lorenz Ng won the S. Weir Mitchell award given by the American Academy of Neurology.

The year also brought the announcement by Dr. Lyman Wynne, Chief of the Adult Psychiatry Branch since 1960, that he will be leaving NIMH in June 1972 to accept the post of Professor and Chairman, Department of Psychiatry, at the University of Rochester School of Medicine. A member of our staff since 1952, Dr. Wynne completed his psychiatric residency and the requirements for a Ph.D. while here. His many methodological and substantive contributions have made him an outstanding leader in clinical psychiatric research. Although we share his pleasure at his selection for the new post, we shall sorely miss his continuing contributions to this program.

My concern for the future has to do with what I consider a serious constriction in our ability to support the basic research to which this program is committed. The vicissitudes of Federal funding are such that it is necessary to make plans a number of years in advance of their implementation. We now have available the new space which we planned ten years ago. When there was still every reason to expect uninterrupted support our laboratories

embarked on a series of studies which would be brought into full operation only after the new facilities became available. The unexpected stresses which beset the nation resulted first in hiring restrictions and then in the loss of many positions needed for the full implementation of the studies which had already begun. Now we are faced with the fact that although we still have a very large program and a large budget, we cannot carry forward with the desirable degree of support all the enterprises we have undertaken, nor is it likely that our budget will be increased to a level which would make that possible in the foreseeable future. With almost every operation stretched to its absolute limit, with many of them pressing for and deserving of additional support, we find ourselves without the flexibility and freedom from external pressures which we enjoyed in the earlier years of this program and which, in my view, are desirable and perhaps even necessary for the highest levels of creative work.

We are faced with the difficult task of trying to cope with this situation in a way which will not prove destructive. At first glance it would seem that the simplest solution would be to cut back those studies which seem on balance to be making the slowest progress, and to divert the resources thus made available to those projects which show the greatest promise for early pay-off. To a certain degree we actually do this, but there is a point beyond which such a practice would become self-defeating. Research is the exploration of the unknown, and not every expedition can come back crowned by notable achievement. Even the luckiest and most successful investigator sometimes returns empty-handed. We could become too cautious and restricted in our undertakings, and limit our studies to those which everyone would consider worth attempting, even if it should prove unrewarding. If we cut back the freedom to gamble and lose, we might in effect find outselves betting on every horse to "show" and never again come up with a winner. Such a course would cut down our productivity and destroy the excitement which has characterized this program in the past.

Another method of coping with the problem might be not to replace investigators who leave the program for other posts. The resources thus freed could be reassigned where they are most needed. In every instance this procedure deserves the most serious consideration, but its limitations are obvious. Those investigators who are selected out of our program by universities and other institutions are often among the leaders in the field; their studies are widely recognized as significant and fruitful. While we cannot and do not attempt to cover every intriguing area in behavioral research, some are central to the thrust of this entire program and cannot be abandoned without serious loss. We would find our program being shaped, in effect, by the institutions who recruit our staff, rather than determined by our own view of what is important.

Still another possibility might be some regrouping of our resources if such arrangements show promise of increasing the effectiveness of the research efforts. The present laboratory structure is the result of decisions made and goals set as long as 18 years ago. For example, there are studies of schizophrenia in three laboratories and in the Office of the Director. Although there is considerable interchange among the investigators involved,

their principal interactions are with members of the groups to which they belong. Since in many instances their studies developed out of these existing laboratory relationships, they obviously serve meaningful functions in the current organization, but a reconsideration of these functions might lead to more powerful groupings in the areas of primary concern.

All these ideas are just that; they and other proposals will be considered during the coming years in our efforts to make the most productive use of our resources.

ANNUAL REPORT OF THE ADULT PSYCHIATRY BRANCH
National Institute of Mental Health
July 1, 1970 - June 30, 1971

Lyman C. Wynne, M.D., Ph.D., Chief

Continuing for a number of years, the program of the Adult Psychiatry Branch has been especially concerned with understanding the nature of mental illness, especially schizophrenia and adolescent personality disorders. These forms of disturbance have been examined in their family context, which has been studied from a number of vantage points: genetics, especially through twin studies; non-genetic perinatal influences upon development; psychophysiologic and perceptual measures of "predispositions" to illness; communicational and transactional variables, assessed in family therapy, through projective tests, and through experimental conjoint problem-solving procedures; clinical and experimental studies of family-role allocations and group processes which especially affect adolescent identity formation and the separation process of adolescents from their families. In these and related studies a dual emphasis has continued to be the hallmark of the Branch programs: exploratory clinical and psychotherapeutic approaches have been used, in combination or in succession, together with systematic and quantitative assessment procedures.

The Adult Psychiatry Branch continues to be organized into a structure of seven Sections and the Office of the Chief. The work of each will be summarized in this report. However, a number of new developments and activities, some still in the process of implementation, are especially noteworthy because of the impact on the Branch as a whole as well as on collaborating investigators. First, after extended construction delays, a new group of experimental laboratories were completed late in the fiscal year for use by the Section on Perceptual and Cognitive Studies and the Section on Experimental Group and Family Studies. These new facilities will substantially strengthen these parts of the program, but also will be a valuable resource for other investigators in the Branch and in other parts of the Intramural Program. Second, the long-term massive data collection in the WHO International Pilot Study of Schizophrenia has been completed by the Section on Psychiatric Assessment, and plans are moving forward for this Section to assume responsibility for running a reorganized psychiatric ward in the Clinical Center, to which acute psychotics will be admitted for intensive research assessment and therapy. It is anticipated that this clinical research setting will facilitate a variety of collaborative studies. Third, important gains have been made this year in the speed and efficiency with which computerized data processing can be carried out, a matter of great importance in five of the Sections and the Office of the Chief. Fourth, the programs of the Personality Development Section and Family Studies Section are being consolidated on a psychiatric ward devoted to treatment of adolescents.

This forthcoming administrative shift will make possible greater efficiency and flexibility for the staff members and clinical team in this program. Fifth, efforts have continued to achieve greater participation in community settings, this year particularly in a District of Columbia runaway house and in a local high school. Sixth, members of the Branch staff have made a substantial input in helping develop the Equal Employment Opportunities Program (EEO), both within the Branch and in the Intramural Program as a whole, particularly through the devoted efforts of Dr. Winfield Scott, Deputy EEO Officer for the Intramural Program.

On the other hand, there have been a number of areas of stress for the Program. Overall, administrative restrictions on budgetary and hiring flexibility have been a source of chronic concern and uncertainty. In carrying out the clinical program, difficulties in obtaining adequate nursing support through the Clinical Center central administrative offices have curtailed clinical work with difficult patients who are especially important to study in Intramural Research. Lack of support for the most capable and experienced nurses is impairing ongoing programs and will make more difficult the new service treating acutely psychotic patients.

With the gradual constriction on funds and positions for supporting personnel and for new needs as they arise, flexibility of program planning has been almost eliminated. Within the Branch efforts have been made to achieve greater flexibility by reconsidering how the Clinical Associates, who are fulfilling military obligations and must be hired four years in advance of their arrival, can fit into ongoing programs which have changing personnel and work needs. In order to free up positions for the future, a decision was reached this year not to hire additional Clinical Associates for the time being, so that some Associates may be invited to continue on the staff after their two years of service and other positions may become open to fill other needs.

Finally, a forthcoming change in the Branch will involve the retirement from administrative responsibilities by Dr. Lyman Wynne on July 1, 1971. He will continue in the Intramural Program during the coming fiscal year, preparing his materials for publication and serving in a collaborative and consultative role with various Branch staff.

OFFICE OF THE CHIEF

Drs. Lyman Wynne and Dr. Margaret Thaler Singer, with the assistance of Mrs. Margaret Toohey, have proceeded with the analysis and interpretation of three large samples of families who have been tested, especially with the Rorschach procedure, in Bethesda, Houston, Texas, and London, England. Data from 681 persons in 214 families have been more fully evaluated with multivariate statistical techniques. The findings and their implications for theory will be reported in detail in the coming year. By using the technique of multiple regression analysis, they have established that the total frequency of communication deviances shown by parents is highly predictive of the severity of illness in their most disturbed offspring. This variable continues to be significant even when the effects of other variables, such as clinical

diagnosis of the parents, social class of the family, age, education of the various family members, and sex of the offspring are all taken into account or "held constant." However, the severity of illness of the parents is also a valuable predictor of the offspring's diagnosis; the clinical diagnosis of the parents and their communication deviance scores include components which are statistically independent of one another and which each separately predict offspring diagnosis with accuracy. The clinical diagnosis of the borderline syndrome in the parents is especially valuable for predicting a sub-diagnosis of process schizophrenia in the offspring. However, the parents of reactive or remitting schizophrenics have high communication deviance scores even when they themselves have been diagnosed as neither psychotic nor borderline.

Analysis of data from a new sample of parents tested in London appeared to suggest, when initially examined by Dr. Steven Hirsch in London, that the word count of the parents while giving their Rorschach responses was a better predictor of the offspring's illness than was the communication deviance scores. However, further analysis of these data has now shown that these results occurred because the English tester failed to administer the Rorschach procedure in a standardized way and systematically influenced the responses of the parents. In the Houston and Bethesda samples of families, word count had no predictive value, overall, when other variables were held constant.

A further evaluation of the communication scores, factor analyzing the 41 categories, plus word count, has shown that these categories fall into 5 highly loaded factors for the parents in such a way that clear evidence supporting a theory of communication in these families, previously formulated by Wynne and Singer, has been obtained. These various data analyses have proceeded to the point where it is now possible to specify and confirm particular hypotheses which show that the communication behavior of the parents of schizophrenics differs from that of the schizophrenics themselves but nevertheless is highly predictive of schizophrenic illness in the offspring.

These methods are also being applied to samples of adoptive parents tested by Drs. Wender and Rosenthal in the Laboratory of Psychology, and will be examined further in prospective longitudinal studies with high-risk families versus low-risk families. Further, in a comparative study with Japanese families, Drs. Wynne and Singer working with Mrs. Mieko Caudill are applying these same methods to the very different Japanese communication patterns. A detailed study of the problems of translating communication samples, as found in verbatim Rorschach records, from Japanese to English, and vice versa, has been completed. This work, conducted with collaborating investigators from both countries, has shown that parental communication samples differentiate parents of schizophrenics from other parents in both cultures. However, the communication patterns need to be assessed somewhat differently in the light of language norms in each of the cultures which affect how speech is implicitly understood in one culture but not in the other. For example, a hesitant, incomplete statement in Japanese is regarded as a communication device for politely inviting the other person to join into the dialogue, whereas the same type of speech, when translated into English, has

a perplexing and sometimes confusing impact upon the listener who is responding in terms of American cultural norms. Thus, those communication patterns which are related to cultural factors can be delineated with these methods at the same time that the principles for differentiating communication disorders associated with a schizophrenic illness in an offspring are similar despite Japanese-American cultural differences.

During the coming year Drs. Wynne and Singer plan to proceed with the analysis and interpretation of their long-term data collection and to link their communication data together with other varieties of family data collected using psychophysiologic and perceptual test measures, obtained in the laboratory testing of the families of normals and of patients, and also with a sample of normal twins. Their writing will be organized around the main themes of family relationships, a reconceptualization of schizophrenia, and the theory and practice of family therapy.

SECTION ON PERSONALITY DEVELOPMENT

The Section on Personality Development, under Drs. Roger Shapiro and John Zinner, has continued its study of adolescents, normal, and disturbed. This program combines investigation of the individual adolescent, of the adolescent together with his family, and of the adolescent in relation to his peer group and adult authority figures. This investigation is conducted with psychiatric patients seen in individual, marital, and family testing and therapy in a residential treatment unit at the Clinical Center and also with adolescents who are in student rather than patient roles at the Sidwell Friends school in Washington, with the cooperation of their families. This year a new group meeting on the psychiatric unit has been initiated for the study of authority relations and peer relations. A classroom study group has been conducted using similar methods at Sidwell Friends School. These methods are also being used by Branch staff in conferences in which intergroup relations are studied. In addition, investigation continues of ongoing emotional changes, measured by galvanic skin response, of family members and therapists while they are participating in conjoint family therapy. A new longitudinal assessment of cognition and identity formation in early and late adolescents is also being done. The follow-up study conducted by Mrs. Carmen Cabrera and Dr. Sheldon Roth of adolescents and their families treated by this section is being continued.

(1) Treatment of disturbed adolescents and their families. Psychiatric unit 3-West continues to be utilized as a residential treatment unit for disturbed adolescents. In addition to three meetings a week of the patients, the nursing staff, and the unit administrator to consider issues of living together, administrative regulations, and work and school responsibilities, a fourth meeting was added this year. This is called the "unit study group." It is attended by all of the patients; by Miss Gay Grover, the Chief nurse; by Dr. Kent Ravenscroft, the unit administrator; and by Dr. Roger Shapiro, the clinical director of the unit. Its task is to study authority relations and peer relations on the unit. Administrative decisions are not made in

the meeting, but patient and staff roles are explored, and efforts are made to elucidate implications of behavior of patients and staff in relation to each other.

The 3-West therapeutic community continues to have an active school and work program with high school classes conducted in the unit by teachers from the Montgomery County school system. In addition to the milieu program, therapeutic modalities employed are individual psychotherapy for the adolescent, conjoint family therapy, and marital therapy. Typical problems for which these adolescents are hospitalized continue to include frequent drug use, particularly marijuana; running away; deteriorating school performance and truancy; impulsive behavior; and depression with suicidal attempts.

A major aim of the investigators is to understand ways in which parental behavior may impair the emerging identity of the adolescent child. Family verbal and nonverbal behavior is studied by observation during family therapy sessions and by scrutiny of typed transcripts of these interactions. A detailed formulation is made of the parent's mental image, or delineation, of his child and of the parental behaviors which communicate the delineation. A major finding is that in disturbed families the parental delineations are frequently more determined by the parent's own emotional and defensive needs than by a realistic perception of the adolescent's personal and highly individual qualities. Adolescents are often quite sensitive to their parents' needs and anxieties and may modify their own self-image to complement or match the parental image which would be least threatening to that parent. The adolescent's awareness that his striving for autonomy may conflict with the psychological needs of his parents may lead to his developing irreconcilable conflicts and disabling emotional symptoms.

In this long-term study new families are continuing to be brought in for treatment and research. Dr. Roger Shapiro and Dr. John Zinner are now reporting the theoretical framework from which they view adolescent disturbance and its relation to the dynamics of the family. These papers include detailed family case studies which discuss the identity problem of the adolescent in relation to the dynamics of parental delineations. Analysis of this material includes a view of the family as a small group and contains inferences about dynamics of unconscious assumptions which cause it to deviate from its primary task of promoting autonomy in its adolescent members.

(2) Applications of Tavistock Group Relations Study Methods. This year an NIMH Intramural Research Group Relations Conference Committee was formed. It consists of Roger Shapiro, chairman; Donald Boomer, Morris Parloff, Winfield Scott, and Lyman Wynne. All of these people have participated in the Washington School of Psychiatry-Tavistock Institute Group Relations Conferences and have been interested in the application of the methods and concepts of these conferences to group and intergroup problems within NIMH. The committee has been planning an NIMH-sponsored Group Relations Conference to study problems within the institution related to implementation of the Equal Employment Opportunities Program. In May, Dr. Pierre Turquet, of the Tavistock Clinic in London, will be a consultant to the committee and will

conduct two 12-session study groups and a series of application groups as an initial exploration of the difficulties encountered in implementing EEO policies in NIMH. His work with these groups will be the basis of further planning for an NIMH Group Relations Conference next year.

The psychiatric unit study group already described is an application of the concepts and methods of the Tavistock conferences in a study of peer relations and authority relations on the psychiatric unit. A parallel classroom study group has been conducted this year at Sidwell Friends School by Dr. Stuart Hauser. He has met with 10 students in the seventh grade plus their homeroom teacher and the principal of the middle school in a 12-session study group meeting weekly for one hour. This group has had the task of studying authority relations and peer relations in the classroom. The group has demonstrated the feasibility of conducting this kind of study in a school situation with teacher, principal, and students all participating. The adolescents participating were considerably younger than those on the psychiatric unit. They were in general easier to involve in active discussion than were the patient group. Comparison is being made of the nature of roles taken and given and the quality of anxiety and the nature of defense evident in behavior in these groups.

(3) The family psychophysiology project. The family psychophysiology project, conducted by Dr. John Zinner with the assistance of Mrs. Deborah Runkle, was initiated to provide quantifiable information about the subjective experience of family members while they are interacting in family therapy. The galvanic skin response (GSR) was selected as the initial variable to be monitored because it has been demonstrated to be a reasonably valid measure of anxiety occurring in a interpersonal context. The technique thus far employed in the project involves the continuous monitoring of GSR of family members and therapists during family therapy sessions. Accurate synchronization of the polygraph record with audio-tapes permits an assessment of physiologic responses of the group and its component members with verbal behavior. In addition, family sessions are recorded on video tape employing a split-screen technique which allows the simultaneous observation of family behavior and concurrent physiologic responses. Playback of these videotapes permits the study of the sequential unfolding of observable behavior and subjective experience as it occurs within family therapy sessions. In particular, family interactions involving intense emotional meaning are identified by psychophysiologic reactivity of the participants. These interactions are isolated and examined to determine the sources of emotional stimuli within the family and the characteristic way in which the family group reacts to stimuli of high emotional valence. For example, when members of one family shared a high degree of physiologic reactivity, the family behavior which followed was of a kind that heightened their psychologic defenses and reduced their psychophysiologic reactivity. The family as a group shared in these processes. Similarly, the intervention of therapists may serve to generate increased family reactivity or may dampen physiologic responsiveness and emotional involvement. The ability of the therapist to sustain family affectivity seems to be determined more by the relevance of his intervention

to the immediate interpersonal or intrapsychic family conflict than by the psychological depth of the interpretation.

During the past year, efforts have been directed at reduction of the considerable amount of data for statistical analysis. In particular, a successful attempt has been made in developing a computer program to retrieve physiologic data on family members which occurs within specifiable categories of family or individual behavior. The first study has involved the examination of physiologic reactivity of family members during periods in which specified dyads are speaking and listening to one another. From this analysis, based on two family sessions from one family of a borderline adolescent inpatient, it is clear that the distribution of physiologic response of any given family member or therapist does not occur randomly, but is dependent upon the identity of the dyad interacting at any given moment in which the session is sampled. In addition, these findings may be constant for particular dyads in the same family across family therapy sessions separated by only a brief interval. Thus, these observations support the idea that certain dyadic interactions within a given family retain a high emotional valence which may relate to the psychological and symptomatic outcome of the index patient within the family.

Additional studies carried out within the project have demonstrated that the physiologic Law of Initial Values, applicable in many of the situations where physiologic reactivity is measured, may not hold for the GSR as it is recorded in family therapy session. Our findings indicate that, with few exceptions, the intensity of physiologic response is independent of the pre-stimulation level of physiologic activity. These findings, now in preparation for publication, greatly simplify the scoring procedure by allowing the investigator to consider the amplitude of the GSR independently from the pre-stimulus basal skin resistance.

(4) Longitudinal assessment of cognition and identity formation in early and late adolescents.

The overall thrust of the studies begun this year by Dr. Stuart Hauser in the Personality Development Section was to broaden and deepen previously developed tools for the measurements of identity formation (Hauser, S., Black and White Identity Formation, N.Y., Wiley, 1971).

Dr. Hauser's previous work concentrated on black and white lower socioeconomic class adolescent boys, following them in their course through high school. His new investigation concentrates on middle socioeconomic class adolescents of both sexes who are of patient and nonpatient status. In addition, early and late adolescents are included in the sample. Thus several contrasts of interest are built into the design: patients-versus-non-patients; early-versus-late adolescents; male-versus-female adolescents; and each of the main groupings (patients and non-patients) can be subdivided in terms of sex and age for intra-group comparisons as well. All of these subjects will be studied over a two-year period, with timed interviews and testing every 6 months.

The instruments for studying the subjects include a self-perception interview, a Q-sort, and a battery of cognitive tests. The Q-sort is a major technique of the study as it focuses on self-image perceptions. Operational definitions of identity variants have been formulated based on Q-sort measure (Hauser, 1971). Innovations in the use of this instrument which have been worked out for this project include new ways of generating the deck of self-descriptive statements, and new methods for analyzing the obtained data. Through these modifications it will be possible to focus more intensively on dimensions of each self-image as well as overall integration and changes in self-images for a subject. The dimensions being studied are "structural complexity" and "relational complexity" as measured by information statistics analyses and interpersonal differentiation as measured by the ratings of different personal sources of self-image components. Thus, both structural and content aspects of self-images will be analyzed as well as correlational analyses of overall fit of images and their changes over time.

The cognitive battery focuses on processes of categorization, differentiation, conceptualization, and problem solving. Parallel changes in cognitive and self-image processes, as well as hypotheses about sequences between cognitive and identity formation processes, will be examined.

To date, the following has been accomplished: (1) Initial interviews and tests are completed on 18 patients and 35 controls (middle socio-economic) from Sidwell Friends School and NIH; (2) data collection #2 has been obtained for 5 patients and 3 controls; (3) self-image data from the previous sample of black and white adolescents has been further analyzed in terms of structural complexity and relational complexity. These new results are now being written up.

FAMILY STUDIES SECTION

During this past year the clinical activities of the Family Studies Section, under Dr. Helm Stierlin, have been increasingly coordinated with the Section on Personality Development. Both programs primarily work with adolescents and their families, using the same residential treatment unit and with many of the same treatment objectives described in the report of the Section on Personality Development. In addition, Dr. Stierlin and the staff of the Family Studies Section have taken a special interest in somewhat younger adolescents, aged 13-15, have engaged in longitudinal and follow-up studies, and have focused on pathological separation processes of adolescents, particularly those showing runaway behavior and tendencies. The Unit on Art Therapy, under Mrs. Hania Kwiatkowska and Dr. James Dent, has continued with a variety of research and evaluative activities.

(1) Longitudinal predictions and follow-up studies of adolescents at high risk for psychopathology: In this study, students with school difficulties at ages 14-16 are regarded as a group at high risk for enduring psychiatric difficulties. The basic objectives of the project are to develop methods and criteria for longitudinal predictions appropriate for adolescents and to test these methods in a five-year predictive study.

Special attention is being given to developing criteria for predicting schizophrenic versus sociopathic (delinquent) outcomes.

Conjoint family interviewing and therapy provide a major means of gaining understanding necessary to make these predictions. At present, most adolescents in this program receive inpatient treatment on Unit 3-West. They are seen three to four times weekly in individual psychotherapy, and other family members receive individual therapy insofar as this appears necessary and/or feasible. The parents are seen in marital therapy once a week, and the whole family meets conjointly once or twice a week.

In addition to being studied through psychotherapy, all family members participate in a variety of test procedures carried out by the staff of other Sections in the Branch. These procedures lend themselves to independent evaluation.

On the basis of these various evaluations, predictions are made about a number of aspects of family development, but especially about the adolescent's life style and psychiatric status at the age of 21. A first prediction, covering ten basic items, is made immediately after the screening interview. Another, more amplified prediction is made after the termination of the treatment. It is expected that the later confirmation, partial confirmation, or refutation of these predictions will deepen our insights and sharpen our hypotheses about the adolescent's developmental and separation process.

As a result of preliminary follow-up interviews (which were carried out by Drs. David Levi and Robert Savard last year) and the ongoing therapy and observation of adolescents and their families, the following major findings and/or formulations emerged.

The first finding concerns the important, though relatively neglected, role of the father in the separation process of adolescent sons. Clinical and follow-up data indicated that the middle-aged father's crisis of integrity frequently overlaps with and aggravates the adolescent son's crisis of identity. Most fathers in this sample suffered an insidious depression at this phase of their lives, often as their own earlier ambitions were fading. Their depression made them unavailable to their adolescent sons at a crucial developmental juncture. These sons consequently were subjected to an intensified symbiotic or incestuous pull from their mothers. This parental constellation has implications for the treatment of adolescent sons in that it makes their fathers' depression appear an important focus for advantageous therapeutic intervention.

Second, the role of parental perceptions and expectations as forces which either induce or inhibit their children's separation was elucidated. Complex and often contradictory parental perceptions about their children's competence and autonomy appear to be major contributing determinants of the outcome of the separation process. A paper which describes these parental perceptions also considers their implications for family therapy.

Third, two patterns of separation in adolescents, called centrifugal and centripetal, were delineated and documented with clinical examples. The patterns reflect forces in the family which are directed either inward or outward from the family. In disturbed families these patterns tend to take extreme forms, altering the separation course of adolescence and providing a contact within which various forms of psychopathology arise. In particular, these observations elucidate those experiential factors which appear to contribute to either a schizophrenic or sociopathic outcome.

(2) Individual and family dynamics of adolescent runaways: About half a million teenage children are believed to run away from their American homes every year. Presently, the individual and family dynamics of this large group of adolescents are insufficiently understood. Our project offered a unique chance to study this patient group and their families in depth. In the sample so far collected 24 out of 37 index patients had run away from home at least one full day and night before they had turned 17 (some of them had gotten as far away as Florida, California and Canada), while the other 13 adolescents had not. In carefully studying the runaway adolescents and comparing them with the non-runaways in our sample, five sub-groups of runaways could be distinguished. These groups seem to represent different family and individual dynamics and hence pose different treatment problems. Particularly interesting was a group of mainly schizoid and lonely runaways with no or marginal peer contacts. Also, we distinguished a group of "abortive runaways" who tended to return quickly to their parental homes.

Further, the examination of adolescent runaway tendencies illuminated parental modes of transaction which cause the separation process to become distorted. Specifically, the modes of binding, delegating, and expelling were described. When a binding mode prevails, there exists a sticky family climate which causes the adolescent's separation to be delayed or aborted. When a delegating mode dominates, adolescents are exploited for various parental ends (such as the providing of vicarious thrills) which requires the adolescents to move out of, and return to, the parental orbit. When the third expelling mode is strong, we find an excessive parental neglect and/or rejection of the adolescent. Adolescents who are exposed to this mode tend to become early separators or runaways and frequently show sociopathic traits. Many of them seem to turn into "street people" and drug pushers.

Since October 1969, Dr. Joseph Herzberg has consulted to Special Approaches to Juvenile Assistance in Washington, D.C., an organization in that city that operates group foster homes for adolescents separated early from their families. As a consultant to the young counselors in these settings (themselves frequently former runaways or current college dropouts in their early twenties), he has collected observational data about adolescent peer group activities in a new kind of setting which is an alternative to the family setting and usual institutions. He has also obtained interview data about the non-professional, untrained youth workers who organize these runaway houses.

Dr. Herzberg has also developed a consultation to the NIAID with their problems of a series of early adolescent children with chronic unexplained fever and long school absences. He has helped establish the diagnosis of factitious fever in these cases and has become interested in the family dynamics with each, as well as the interesting intrapsychic dynamics of the patients and their parents. This work will be reported in a forthcoming article.

(3) Adolescent drug users: The study is still in a stage where the individual and family dynamics of drug abuse are observed and various material is collected. It appears now that formulations similar to those described for runaways can also illuminate different groups and family dynamics of drug abusing adolescents.

(4) The phenomenology and dynamics of psychological exploitation: The prolonged therapy and observation of a small number of families with troubled adolescents have provided useful insights into the dynamics of psychological exploitation. In the context of this project, Dr. Stierlin has further elaborated ideas on the function of psychologically internalized objects and on a series of related topics. Also he has studied the dilemma of creative artists who are torn in their loyalties toward various values and (mainly internalized) human figures. (The German poet Hölderlin who turned schizophrenic in his thirties was singled out as an example illuminating some of these dynamics.) Dr. Stierlin continues to work on his monograph on the subject of psychological exploitation and liberation.

(5) Studies of the Unit on Art Therapy: The collection and ratings of material for the Dent-Kwiatkowska Systematic Analysis of Family Art Evaluations has been completed as of April 1971. Ratings of pictures and the punching and editing of data cards were completed, as follows: (1) over 1,500 pictures from seventy families to be analyzed by diagnosis of the index and other variables, (2) 500 of these pictures rated twice for studies of interrater agreement, and (3) an additional 300 pictures from second family art evaluations for studies of stability and change over time.

Analyses of interrater agreement and stability over time have been conducted and will be reported in articles summarizing our general findings. Also studied were the individual biases of our raters and their preferences for particular pictures. This last analysis was reported at an international symposium on empirical aesthetics in Glasgow. Further analyses will be conducted upon the completion of Dr. Dent's standardized description of the seventy patients.

A replication of this project by the Institute of Psychology at the Catholic University in Rio de Janeiro, Brazil, the ratings of ten families have been completed and cards have been punched in Brazil. The computer analysis, to be carried out by Dr. James K. Dent at NIMH, will define the findings within the next few months. Studies of interrater agreement in the scoring

of 68 randomly selected pictures drawn by American families are being carried out using an American bilingual rater and Brazilian raters in Brazil using the manual in Portuguese translation. The items where there is a significant discrepancy in the interrater agreements will be studied to evaluate whether the source of the disagreement is of linguistic or cultural nature.

Family Art Evaluations have continued with most of the patients and families admitted to the Family Studies and Personality Development Sections during the past year. In these families, mostly with adolescents with behavioral problems such as delinquency and drug usage, the family pictures, verbal comments, and nonverbal transactions revealed the concreteness and apparent clarity which masked a paucity of emotional content. Also noted frequently was a denial of serious marital difficulities and the projection on the patient of the parental problems.

Special attention was given this year to the youngest sibling, age 8 to 14, participating in the family art evaluation sessions. The pictures of these family members revealed emotional problems ranging from depression and severe anxiety to underlying psychopathology, contrasting with their apparent uninvolvement in the family difficulties.

A therapeutic art class continues to be conducted by Mrs. Marilee Shapiro for patients and staff on the adolescent treatment ward. Different techniques stimulating free art expression are introduced in this class. The class has been useful in bringing the nursing staff into a creative activity with the patients.

Interest in art techniques with families by clinicians and researchers outside of NIMH noted already in the year 1969-1970 has considerably increased this year. Seminars have been conducted by Mrs. Kwiatkowska for different psychiatric training centers which plan to introduce family art techniques on the NIMH model, in their clinical, research or training programs. Among them were the Menninger Foundation and the Washington School of Psychiatry. Workshops have also been conducted at NIMH for graduate social work students of the Catholic University in Washington, D.C., for the Mental Health Associates trained at Montgomery College, for art therapists on the occasion of the first convention of the American Art Therapy Association, for art therapists in training at the Hahnemann Medical College, George Washington University Hospital and for nursing and recreational staffs of the National Institute of Health.

SECTION ON PSYCHIATRIC ASSESSMENT

The goal of the Psychiatric Assessment Section under Dr. John Strauss, Chief, is to develop diagnostic concepts and categories that will have more meaningful relationships to etiology, course of illness, and response to treatment, than diagnostic systems currently is use. The need for improved diagnostic categories has been amply documented by the numerous research efforts in the epidemiology, treatment, psychophysiology and biochemistry of psychiatric disorder that have been hindered by the lack of reliability and validity of the currently used diagnostic categories. The staff of the Psychiatric Assessment Section employs standardized clinical interviews, alternative diagnostic models, cross-cultural comparisons of psychiatric syndromes, and measures of course of illness, to develop more meaningful diagnostic categories.

International Pilot Study of Schizophrenia: One major activity of the Section has been participation as the United States Field Center in the International Pilot Study of Schizophrenia (IPSS) sponsored by the World Health Organization. Other collaborating centers in this project are located in Colombia, Czechoslovakia, Denmark, India, Nigeria, Taiwan, the United Kingdom, and the USSR. The goal of this study is to develop and utilize cross-culturally applicable interview schedules for the evaluation of psychiatric patients in different countries. These schedules can then serve as a basis for future studies of comparative epidemiology and the cultural and biologic factors in psychiatric disorders. Collaborating investigators from the centers have cooperated to develop the interview schedules for eliciting information on current psychiatric status, psychiatric history, social functioning, and demographic background and status at time of follow-up examination. To accomplish this, schedules were written, pretested, revised and retested until they were suitable for use in all of the participating countries.

In the past year, data analysis has been carried out on interviews from 1,202 patients seen in the participating countries. Two-year follow-up interviews have been performed on these patients using forms developed in the study for evaluating course of illness and changes in social functioning. Information obtained from the follow-up investigation will provide a basis for comparing the course of illness of patients with different symptoms and different forms of treatment in culturally diverse countries.

In this study, standard psychiatric assessment techniques have been used for the first time in both initial evaluation and follow-up on a large scale by local investigators in several different parts of the world. Cross-cultural data on similarities and differences of patients from these countries have been obtained. The initial data analyses are being completed in the preparation of Volume I of the report of the IPSS.

Methodology for Analyzing Data for Psychiatric Diagnosis: The Psychiatric Assessment Section, together with Dr. John Bartko of the Theoretical Statistics and Mathematics Group and Mr. Fred Yamada of the Division of Computer Research and Technology, have evaluated and adapted

clustering techniques for defining types of psyciatric patients. Such clustering techniques are minimally influenced by theoretical bias, and let the data itself define the "natural groups" that constitute the patient population. The application of cluster techniques to psychiatric data poses many serious problems arising from both the mathematical properties of the techniques used, and the way in which clustering techniques reinterpret the usual clinical diagnostic modes. In the past year, the investigators have defined more clearly the nature of some of these problems, and developed a clustering technique that gives promising results when applied to the data from the patients seen in the International Pilot Study of Schizophrenia. Using clustering techniques in this way has provided a valuable alternative to customary clinical diagnosis, and clarified some important similarities and differences between types of patients seen in the nine centers represented in the IPSS.

Comparative Study of Diagnostic Systems: Four different diagnostic systems are being evaluated using past psychiatric history and status at the two-year follow-up as criteria for the validity of diagnostic types. The four diagnostic systems being investigated are: (1) clinical diagnoses using the APA Diagnostic Manual; (2) computer derived clinical diagnoses developed by J.K. Wing in London; (3) Lorr's Psychotic Types based on the In-patient Multidimensional Psychiatric Scale; and (4) clusters of psychiatric patients developed from the cluster techniques described in the preceding paragraph. The four diagnostic systems depend primarily on symptom and sign information in placing patients into diagnostic categories. To evaluate the patients from other points of view, a "prognostic" scale and "outcome" scale were developed to "predict" symptomatology and course of illness, and to define level of function at a given point in time following the patient's hospitalization for psychiatric disorder. Initial results indicate that none of the four diagnostic systems are able to predict significantly two-year follow up status nor to postdict earlier psychiatric history. On the other hand, use of multiple regression techniques demonstrates that prognostic items correlate highly with follow up status. These preliminary results replicate results of other studies regarding the relationship of past history to future outcome, but also suggest the lack of utility of several diagnostic systems for the prediction of outcome. In the coming year, these data will be analyzed using a larger sample of patients. The usefulness of the diagnostic systems, and of outcome measures as a criterion of diagnostic validity will be further evaluated in the coming year by the addition of tests of thinking disorder and of psychophysiological, and biochemical variables as external validation criteria to be performed with a new sample of patients. Beginning July 1971, the Psychiatric Assessment Section will assume administration of a Clinical Center ward for acute psychotic patients. This facility will permit more intensive evaluation of concepts and diagnostic categories of psychiatric patients using the methods described above.

Depressive Symptomatology: Another study in which this Section has been involved has been that directed by Dr. William Carpenter. He has used standard assessment techniques to evaluate manic-depressive patients to determine in what way these patients are symptomatically similar or different from schizophrenics. When an adequate number of manic-depressive

patients has been evaluated, the data will be subjected to cluster analysis in an effort to identify groups of patients on the basis of symptom clusters. The relationship of these groups to diagnostic categories will be studied. This will permit a fresh look at the diagnostic process and concepts involved in the sub-categories within functional psychosis. Cross-cultural comparisons will also be made with data from the WHO IPSS described above. Special attempts will be given to the groups designated as schizo-affective schizophrenia to determine the relationship of these patients to manic-depressive and schizophrenic disorders.

SECTION ON TWIN AND SIBLING STUDIES

During the past year the Section on Twin and Sibling Studies under Dr. William Pollin has continued its work in three major long-term studies: the review of data from the twin registry of the National Academy of Sciences; the analysis of data, especially biochemical, in the study of identical twins discordant for schizophrenia; and the longitudinal study of identical twins followed from birth.

(1) Psychopathology in NAS Sample of Twins: In the first phase of studying the twin registry of the National Academy of Sciences, computer-stored diagnostic data was analyzed about 15,909 pairs of male twins who were born in the decade 1917-1927 and who both served in the U.S. Armed Services.

A second phase of data analysis has not been completed in which each twin's Armed Services/VA folder was reviewed. These folders contain compilations of original medical records, evaluations, claims, and multiple other contacts and records. Eight hundred and forty such charts have been systematically reviewed this year by a three-man psychiatric team, after preliminary screening by other Section personnel. These represent all 420 pairs in which one or both twins have received the diagnosis of schizophrenia or any other psychosis. As a result of this chart review, a substantial number of changes were made with regard to zygosity (59 pairs--14%) and diagnosis (160 pairs-38%).

The two major findings of interest were: (a) a strong indication that genetic factors play a significantly greater role in the pathogenesis of affective psychosis than in schizophrenia, and that schizoaffective schizophrenia is closer to affective psychosis in this regard than to other forms of schizophrenia; and (b) an upward revision of our previously-reported concordance rate for schizophrenia in MZ twins. The revised rate, however, remains consistent with our earlier conclusion that there is a definite genetic factor involved in the pathogenesis of schizophrenia, but one that plays a lesser role than previously believed. The data relevant to these points are as follows: for schizophrenia, 26 of 95 MZ pairs (27.4%) and 6 of 125 DZ pairs (5.7%) are concordant. The MZ/DZ ratio is 5.7 and H=.373. In contrast, for affective psychoses, 5 of 13 MZ pairs (38.5%) and none of 27 DZ pairs (0%) are concordant. To make possible computation of an MZ/DZ ratio other than infinity, we assume the next DZ pair would be concordant and the MZ/DZ ratio then becomes 10.8 and H=>.556. If we separate out schizoaffective cases, they show a pattern much more similar to affective than to schizophrenic psychoses with respect to these distribution variables.

Seven of 14 MZ pairs are concordant (50%--the highest concordance rate demonstrated) and none of 12 DZ pairs are concordant, thus again the MZ/DZ ratio is infinite or at least greater than 6.5 if we again assume the next DZ case to be concordant, and H=>.612.

Earlier studies in the literature, suggesting a stronger genetic factor in the pathogenesis of affective psychosis as compared to schizophrenia, have not had the desirable sampling characteristics and large N cohort, selected by uniform screening methods, of this NAS twin pool. Thus, these findings are perhaps more conclusive than others previously reported. These findings appear consistent with the interpretation that there appears to be a better defined, relatively more simple set of biochemical phenomenon related to mood change and pathology, and to affective psychosis, than is the case for schizophrenia where more complex possible biochemical factors appear to be interacting with a greater number of more complex, interpersonal, interactional, and life history phenomena. One might, therefore, anticipate that this more simple and direct biochemical mechanism in the affective psychoses would show a more clear degree of genetic control.

We are now reaching, for the first time, a point which we had hoped to achieve somewhat earlier, where we are able to screen this NAS sub-group of psychotic patients to locate sub-samples with whom issues of genetic and non-genetic specificity could be evaluated. A preliminary screening completed before we had identified all of the affective psychosis group, the smallest limiting group, suggested that we will not be able to obtain enough such subjects from this pool to satisfy our needs. For that reason, we have begun to solicit nationwide for MZ cases discordant for affective psychosis, as well as other possible control groups. The initial response has been very slow, but not enough time has as yet passed to enable us to determine whether we will be able, by either of these means, to obtain the desired but very rare subject population we are looking for.

(2) Identical Twins Discordant for Schizophrenia: The analysis of data from the study of identical twins discordant for schizophrenia has continued. Data recently analyzed indicates that suggestions presented in last year's report, concerning a possible genetically determined biochemical substrate of psychosis, manifesting itself in abnormal catecholamine metabolism, must be treated with more caution until further work has been completed. It was previously pointed out that a high intraclass correlation coefficient for the catecholamines suggested a high degree of genetic determinism and that the catecholamines and their metabolites previously evaluated were elevated (with respect to group means and distributions) in both the schizophrenic indexes and their non-schizophrenic controls (in the discordant twin series), whereas, the 17-hydroxysteroids were only elevated in the indexes. This finding was integrated with a variety of other evidence suggesting that over-activity of catecholamine systems somewhere in the CNS may be a common factor contributing to pathogenesis of a variety of types of psychosis and might specifically be related to that phase of schizophrenic and affective psychoses which clinically is expressed in agitation, panic, and their derivatives.

However, it has now been determined that MHPG, the catecholamine which current evidence indicates is most closely related to, and the best measure of, CNS rather than peripheral catecholamines, is the catechol substance measured in these subjects which does not demonstrate the previously described pattern. It is not elevated in the schizophrenics, and does not show the same high intraclass correlation coefficient. Further studies will be required to re-evaluate the possible relevance of the initial hypothesis and the current MHPG findings to schizophrenia and psychopathology.

(3) Longitudinal Study of Newborn Twins: The longitudinal study of intrapair differences in MZ twins studied from birth continues to appear to be a promising approach to the study of personality development and character formation and also is relevant to understanding the determinants of some of the life history patterns and early childhood characteristics which our schizophrenia study has suggested play a significant role in determining the pathogenesis of severe psychopathology. This year, 5 of our initial cohort of 10 twin pairs reached the age at which they could be studied in the Child Research Branch Experimental Nursery School. They have also had projective testing (Rorschach), developmental testing (Bayley), neurological evaluation, and child psychiatric evaluation. (Two of these first five sets are dizygotic controls.)

Congenital endowment and early competence: The physiological endowment, early adaptation, and overall competence during the first week of life were scored by a new technique, First Week Evaluation Scale (FWS), which rates each of the following variables from 1 (worst, requires specific attention) to 5 (best, normal): health, physiological adaptation; calmness, vigor; attention; and neurological examination. The ten children were divided into three classes on the basis of these FWS: high, middle, and low FWS groups.

Nursery school behavior: The Nursery School staff and observers had no previous information about the children or their first week status. In the school, the child with the high FWS coped well, talked well, and was curious and exploratory. His play was original and highly structured, involving home-situation themes and other sequential activities, in which he was highly involved, and yet he was able to take the leads suggested by the adult (tractable). The low FWS child was markedly more fearful and less talkative. His play was less organized, gross, rough, and flitting. His behavior was more frenetic, he did not achieve the ends he wanted, and he showed difficulty in delaying his behavior to achieve an end.

Rorschach behavior: The Rorschach test was administered to each of the children at about age 3, by an experienced tester with no previous knowledge of the life histories, birth order, or any other information about the children. The examiner completed a newly devised rating scale evaluating the children's general behavior during the testing rather than scoring the content of their verbal productions as such. The Rorschach behavior was

consistent with the nursery behavior: the high FWS group was more competent, talked better, and was more motivated; the low FWS group was more fearful and showed more difficulty in the control of behavior.

Developmental testing, psychiatric evaluation: The Bayley developmental quotients of the high FWS group were within the top half for all the cohort, the low FWS group scores were in the lower half. Psychiatric evaluation revealed that 3 out of 3 of the low FWS group had significant speech difficulties, including stuttering, baby talk, and lisping. All three high FWS children had unusually well-developed language skills, without any articulation problem. All three of the high FWS children were mature, outgoing, and imaginative youngsters who were independent, well-organized, and yet not obsessively constricted. Two out of three of the low FWS group were remarkably immature youngsters, one being quite frightened and the other unusually silly and infantile.

Developmental course: The longitudinal, in-depth study of the children and families, the results of the FWS, nursery school, Rorschach testing, developmental assessment, neurological evaluation, and psychiatric evaluation are all consistent with the interactional view of child development, in which the course of development is seen to be the result of a variety of determinants, including constitutional (genetic, uterine, perinatal) and experiential factors. The psychodynamic study of the families has revealed the importance of early neurological and physiological competence in shaping the child's pattern of responding to the environment and to internal stimulation. Similarly, the data indicate the importance of the family's response to the child's needs and to ways in which parents can shape the behavior of their children.

The data also increasingly leads us to an interest in psychophysiological and stimulus-processing phenomena. It is this interface between congenital endowment and familial environment which seems responsible for the formation of personality individuality in the twins.

SECTION OF CLINICAL PSYCHOLOGY

Research activities of the Section on Clinical Psychology relate to the development of psychological tests as clinical tools, modification of tests for research purposes, and applications of the tests to a variety of problems which relate to the study of psychopathology. Psychological tests, including projective techniques, tests of intelligence and of central nervous system functioning, are a major source of data for research efforts of the Section. All patients admitted for treatment through the Adult Psychiatry Branch are psychologically tested, as are their parents and selected siblings as well. The families are tested with consensus procedures as well as individually. Besides APB patients and their family members, selected patients admitted to the Clinical Center by other Laboratories have been psychologically tested for both clinical and research purposes. These include especially patients with affective disturbances and patients with a variety of neurological problems.

A major activity in the area of test development involves the use of the Consensus Rorschach and the playback of taperecordings of the procedure to the subjects. In this work, applications of the technique for clinical assessment of families are being explored and developed. At the same time, systematic research is being done on the differentiating features of families of psychiatric patients, and on the effects of a variety of "feedback" (by replay of taperecordings) conditions on task performance and on self-image. In a departure from usual clinical procedures, families are engaged as active participants in the assessment of their own functioning. During the first of a series of three sessions, four members of a family - both parents, index and the sibling closest in age to the index - take part in the Consensus Rorschach. They are required to see how many agreements they can reach about what an inkblot looks like, and following that, working individually, to indicate on a photograph of the blot what agreements have been reached. The session is both videotaped and audiotaped. Each participating family is randomly assigned to one of four feedback conditions: videotape replay with two examiners present; videotape replay with no examiner present; audiotape replay with examiners present; and no feedback. Families assigned to one of the first three conditions are instructed to examine their own behavior and the consensus session in an effort to understand the effects of their individual actions and reactions on the family's performance on the task of reaching agreements about the inkblots. At sessions where the examiners are present, it is their task to hold the family to a focus on the effects of their behaviors in the test situation. During the third session, the Consensus Rorschach is repeated, and measures of self-image - which were first administered before the first session - are repeated. The project may result in a technique useful to apply as a part of the clinical evaluation of families prior to their beginning in family therapy. It is likely that performance in the consensus and feedback procedures will have prognostic value for their ability to make use of psychotherapy, revealing something about how the family engages in the process of regarding themselves as a group which affects its individual members.

In a study of patients with severe affective disorders, test response patterns which differentiate among the disorders are being identified. Of special interest is the difference in test performances between patients with unipolar depressions and those with bi-polar depressions. While these patients are difficult to distinguish by outward appearance alone, there are reliable differences between them in performances on both objective and projective personality tests. For example, there are differences in MMPI profiles and in approaches to Rorschach responding between these groups of patients. These differences permit a classification of patients which corresponds to classification of the same patients from more complicated and extensive clinical and laboratory data. During the current phase of this research, effort is directed entirely at differentiation of test response patterns which correspond to clinical diagnosis of patients. At a later stage, however, test performance will be related to historical and prognostic data as well.

Work continues on studies of deficits in intellectual, personality and central nervous system functioning in contrasting groups of patients including epileptics, manic depressive psychotics and some schizophrenic patients. Of special interest in this work in its current phase are contrasting patterns of deficit among these groups of patients in measures of central nervous system impairment. A major aim of the work is to study the relationship between organic and psychological symptomatology in a variety of neurological and psychiatric disorders, and to study the effects of drugs on patterns of deficit.

In application of individual projective techniques to research on psychopathology, two contrasting approaches to Rorschach responding have been identified. The first, the "recognitory" approach, is one in which subjects tend to respond to qualities of the blots with associations to things previously seen. In the "interpretive" approach, on the other hand, subjects attribute qualities to the blots which are not intrinsic in them, qualities such as movement and depth, and these become important determinants of responses, along with intrinsic qualities of the blots. These approaches have been identified in normal subjects, and there is evidence to indicate that it differentiates among different groups of psychiatric patients as well. For example, while uni-polar depressed patients in general demonstrate an interpretive approach, bi-polar patients, both manic and depressed, consistently take a recognitory approach to inkblot responding. There is some preliminary evidence to suggest that the approaches may also differentiate groups of schizophrenic patients defined by patterns of symptoms observed clinically.

SECTION ON EXPERIMENTAL GROUP AND FAMILY STUDIES

This Section, headed by Dr. David Reiss, has developed two major and interrelated objectives. First, the Section studies the reciprocal relationship between family interaction and the thinking and perception in individual family members. Central to this extended study is the development and testing of a theory of consensual variety which states that each family has a characteristic way of collectively construing or experiencing its environment; this consensual experience is the major link between its style of interaction on the one hand and the modes of thinking and perception in its members on the other.

In order to test this theory, the Section has been developing objective, experimental methods for studying subtle, subjective experiences in families and groups.

However, these experimental methods and their results have posed special questions for currently accepted principles of validating experimental findings; therefore, a second major enterprise of the Section has been to reconsider and revise existing theories of experimental design and validation. This critique of theoretical principles has, in turn, generated a series of specific hypotheses and experiments to test them.

Consensual Experience in Families. The basic notion of the theory is that when families are faced with strange, threatening or ambiguous situations, as a group, they will form shared constructs or organized explanations of their environment and their place in it. Further, if a family's characteristic kind of construct can be determined, then a great many of its responses in problem solving situations can be predicted. Moreover, a given kind of construct requires corresponding perceptual and cognitive resources in its members. In the past, evidence had been collected that suggested that such constructs might be defined by three basic dimensions: comprehensiveness and detail; coordination or sharing among family members; and continuity through time. This year, the theory was elaborated in two major respects. First, detailed hypotheses were constructed concerning the relationship of these three dimensions of family constructs to specific forms of family interaction and specific cognitive and perceptual styles. Second, similarities between shared construing in families and analogous phenomena in groups of unrelated individuals were spelled out.

An experimental study, completed this year, helped to clarify aspects of this theory. It has been argued that a family's perception of its immediate environment--say a test situation--may be a product of psychologic deficit in one member, particularly the child. For example, if the family knows or senses the child is psychologically defective, it may perceive the environment as more threatening and react defensively. We sought experimental control of psychologic deficit by a double-blind administration of secobarbital to the offspring. The evidence strongly suggested that the acute psychologic deficit so induced may intensify preexisting perceptions but it does not modify their basic character (e.g., it will not convert thrust into suspicion).

Continued progress has been made in refining other methods for studying shared construing in families and its relation to individual perception and thinking. Following a successful experiment last year, we have completely reprogrammed an on-line teletype procedure. In addition, the Section finished work on three new procedures for studying shared construing: A figure-placement procedure in which the family works separately and together to place animate and inanimate figures on a grid; a map-marking procedure to elicit a family's shared construction of its neighborhood; and an adaption for family use of Rotter's locus of control scale. There is a continuing search for methods to monitor the thinking and perception of individual members while they interact with their families. One such procedure developed by Dr. Richard Stillman of this Section, in collaboration with Drs. Buchsbaum and Pfefferbaum, is an on-line device for measuring eye movement patterns. This could be adapted for monitoring individual perceptual functioning during a family problem-solving task.

Revised Principles for Experimental Design and Validation. In order to test the major hypotheses of the theory of consensual variety, objective procedures must be designed to assess validly complex, subjective states in individuals and groups. The direction of such experimental work should be guided, it was felt, by broad principles of experimental design and validation formalized insofar as possible. With this goal, Dr. Reiss has begun to apply and develop concepts derived from the work of Suzanne Langer. In particular, he has used her notion of "presentational form" as a logical base for interpreting complex creations which are produced by subjects during experiments. The formalization of theory is proceeding along two lines. First, the theory specifies that experiments should be designed to encourage the subject to take standard raw materials and build, construct, arrange or express an inventive, personal and originative product or composition. In the Section's experiments, the family's complex card sorts, picture arrangements and pattern hypotheses are regarded as compositions. The procedure is thoroughly objective since the compositions themselves, or precise analog replicas of them, are the raw data and are subjected directly to quantitative analysis. The major problem, once the experiment is complete, is validating interpretations based on such analyses. Dr. Reiss has begun work on three principles for validating interpretations concerning the experiential states which the subject is trying to present in his compositions. These principles are: portraying the composition, analysis of configuration, and interpretative dialogue. They bear a number of formal similarities, respectively, to content validation; convergent, predictive and discriminate validation; and construct validation.

A large project was completed this year which makes use of some of these notions of experimental design and validation. The project sought to determine how the value orientations and group affiliative styles of psychiatric personnel determine their interaction with patients on psychiatric wards. With NIMH personnel serving as subjects, triads of a doctor, nurse and patient were formed and were required to solve a number of challenging problems of patient assignment. Their solutions were expressed in a series of card sorts, each card representing a patient on a psychiatric ward. These sorts were regarded as the subjects' composition. Analysis of changes

in the configuration of the compositions revealed clear-cut effects of both independent variables: value orientations and group affiliative dispositions. The findings strongly suggest that discrepancies between nurses and doctors in either value orientations or group affiliative disposition make it difficult for them to perceive and structure problems in the same way. It produces a sense of estrangement between them and makes each ready to accommodate to the view of the patient, whom they both perceive as estranged. Thus, both members of discrepant nurse-doctor dyads accommodate to patient views but remain estranged from each other.

SECTION ON PERCEPTUAL AND COGNITIVE STUDIES

The work of this Section has been conducted during the past year chiefly by Dr. Adolph Pfefferbaum, with the assistance of Mrs. Catherine King and Mrs. Carolyn Gruner; substantial collaboration with Dr. Monte Buchsbaum of the Laboratory of Psychology and Dr. Richard Stillman of the Section on Experimental Group and Family Studies has been essential to this program.

The major emphasis of this program has been the development of objective measures applicable to the study of sensory, perceptual and cognitive phenomena. At present, this endeavor is especially concerned with "normal" populations but will eventually have special relevance to the understanding of schizophrenic and other psychopathologic processes. One of the major efforts has been directed toward exploring the use of average cortical evoked responses (AET) to external stimuli which have varying physical and psychological properties. It is felt that this neurophysiologic measure, which requires no volitional motor or verbal responses from the subject, has many advantages as an objective measure for the study of perceptual processes, especially in subjects with impaired capability to respond verbally or motorically.

In collaboration with Dr. Monte Buchsbaum of the Laboratory of Psychology, the concept of "stimulus intensity control" has been extensively examined. Currently, this work is being pursued in normal populations and in several groups of subjects with relevant pathologies, especially endocrinopathy and manic-depressive illness. The studies involve both the comparison of individual and group differences and the study of changes linked to pharmacologic and psychologic variables.

The question of the heritable nature of perceptual, cognitive and neurophysiologic functioning has also led to the current study of this concept in a population of normal twins. During the past year the first twenty twin pairs in this study were tested. The preliminary findings indicate that the cortical evoked response wave forms and amplitude changes, with changing stimulus intensity, are substantially more similar in the monozygotic twins than in the dizygotic twins.

Another major effort is the investigation of the concept of "scanning." This has special relevance in understanding how visual information input is accomplished. A unique and sophisticated computer-run eye movement monitor

has been developed and is now fully operational. Dr. Richard Stillman has been a primary collaborator in this project. Initial results indicate that there are indeed individual differences in eye movement strategies which are consistent from test to retest. This too has proved to be a useful objective measure related to the study of the perceptual process and is being included in the heritability study of the twin population. Previous studies, with more indirect and less reliable indices of "scanning," indicated that schizophrenics fall into subgroups of hyperscanners and hypo-scanners, but that chronically institutionalized subjects, schizophrenic or not, tend to be minimal scanners. Thus because this dimension may be influenced by environmental influence, it is especially important to see to what degree it is also under genetic control.

1971

Annual Report of the Child Research Branch

Division of Clinical and Behavioral Research

National Institute of Mental Health

Richard Q. Bell, Ph.D., Chief

Longitudinal studies are difficult to describe because the phenomena with which they deal are themselves complex. Add to this the fact that this branch assigned each of four phases of development to a different research team, that these research teams all carried out preparatory studies as well as the main longitudinal study, that some have completed their data collection in the main longitudinal study, while others are still engaged in data collection, and that some are still publishing reports on preparatory studies, and it becomes apparent why a report of this kind could easily leave the reader confused.

First of all, for those not familiar with the past history of the longitudinal study, its purpose and methods will be briefly recapitulated. The purpose of the study is to replace retrospective reconstructions with actual data on the sequence of events by which social, emotional, and cognitive behaviors develop in the early phases of the life cycle, covering early marriage through early childhood. A secondary purpose is to make it possible to specify whether certain characteristics of parents preceded or were a reaction to those shown by a child. The strategy is to study husband and wife characteristics prior to the birth of the first child, and the child's characteristics early in life before they had been modified by the family environment. One research team studied the newlywed period and carried out further follow-ups of the marriage as such. A second team studied pregnancy and parent-infant interaction in the first year of life. A third studied only the newborn period. The early preschool and school-age child was studied by the fourth team. Each team of specialists selected the content to be studied and methods to be used at a given stage. Nonetheless, these selections were guided by the goal of eventually integrating data across stages.

Following the above plan, the four teams were organized and completed preparatory investigations by 1965, after which the main longitudinal program was launched. The studies of early marriage were carried out between 1966 and 1969. Studies of pregnancy, newborns, and young infants were completed between 1967 and 1970. Studies of the preschool period were started in 1970 and will continue until 1973. Out of approximately 2200 marriages studied with questionnaires, 870 were also studied intensively with a battery of tests, interaction situations, and interviews. From the intensively studied sample, 135 mothers were interviewed during their first pregnancy, 113 newborns were studied in order to detect congenital characteristics, and 120 cases have been followed up in home and laboratory

observations with their mothers at three and eleven months post-partum. Forty-five children from this series have already been studied at the preschool period, and at this same time a third assessment of the marriage is being carried out, the other having been completed near the second year of marriage.

Office of the Chief

Turning now to this year's activities in each component of the Branch, the first in a series of biennial pamphlets was prepared for distribution to all interested scientists in fields related to the longitudinal study. This pamphlet is needed to answer an increasing number of requests for information on findings coming from preparatory studies, since even these studies of more limited time segments are themselves quite unique. It is also necessary to advise others of the status of various studies in the main longitudinal program, so that they know when to expect reports. The pamphlet also provides the names of investigators who may be contacted for lists of reports that have already been prepared and are available for distribution. Since each team publishes its reports in journals specializing in a given subject matter, reports may be found in all kinds of journals, such as those dealing with marriage and the family, psychiatry, and child development. Without such a biennial pamphlet the interested reader could not follow the course of the study in any single set of publications.

In addition to the biennial report, a general summary of aspects of the longitudinal program relevant to adaptation and stress has been prepared for inclusion in reports of a WHO symposium on this subject that will be given international distribution.

The first step in organizing the data bank for the main longitudinal study was also completed this year. A summary tabulation is now available showing the tests, procedures, and interviews obtained for all subjects at all phases of the study finished to date, including information on completeness and adequacy of the measures obtained. This was an extremely difficult task. Some subjects were seen in one phase and not in the next. Some couples were initially studied as newlyweds, others for the first time in the second year of marriage. Some newborn cases were obtained from outside the longitudinal cohort to fill in the main newborn sample. From this tabulation, any investigator can determine the size of samples with complete data available for any analysis, and the necessary case numbers to locate material at any given phase.

One of the continuing research interests consists of conceptual and methodological developments required to revise socialization theory so as to include child effects on parents. Two papers have been prepared this year along these lines, one elaborating the way children create problems of adaptation and stress in parents, and the other summarizing new research approaches that can be used to isolate the effects of children and parents on each other.

Section on Family Development

Although personnel from this section will be engaged until 1973 in the third marriage follow-up, taking place at the time a couple's child completes the preschool studies, all other data collection on marriage has been completed. Data from all questionnaires, an adjective check list, and from an experimental interaction procedure at the newlywed period, has reached the stage of dimensional analysis. Data from a second interaction procedure used at the two-year follow-up will have been coded by this fall. One report has already been prepared on data from the newlywed period, consisting of an analysis of the dimensions of adjectives used by husbands and wives to describe each other.

In the last annual report I mentioned a system that has been devised to code for ready computer retrieval a vast amount of qualitative information on the premarital and marital histories. A further step is now being taken, consisting of the analysis of functionally equivalent bits of qualitative information in these histories.

Two steps have been taken this last year to protect the marriage records against accidental loss or fire. These are important steps because the marriage records are not only the source data for our own present longitudinal study, but a reservoir of information for future longitudinal studies that may require a still longer time span for the emergence of certain characteristics, and which require a relatively large source sample. Scores for all questionnaires and codes for the interaction procedure at the newlywed period are on magnetic tape. Marriage history data are being microfilmed.

Despite the amount of time the marriage staff has had to devote to the analysis and safeguarding of a vast amount of marriage data, they have published six interesting and valuable contributions to the research literature on marriage this year. John Kafka has reported a reformulation of Jackson and Bateson's double-bind hypothesis in a paper that seems to be leading to a radical revision of our previous thinking about family communication. David Olson has published a survey and systematization of marriage and family therapy approaches and an initial report on the new family interaction procedure developed for our two-year marriage follow-up. Kafka and Olson have joined with Robert Ryder in a paper that reconstructs the process of courtship in the context of an overall scheme for thinking about joining and separating influences in marriage. A novel hypothesis developed in the latter paper is that there is an alternation phenomenon shown by friends and relatives of a young couple, such that in early phases they facilitate the relationship, while in later phases, as its serious implications become apparent, they are often found in opposition to the relationship.

Section on Parent-Child Behavior

The next team to be in contact with the subjects from the main longitudinal series was the Section on Parent-Child Behavior. With one exception, data collection on all phases for which this team is responsible, from

pregnancy through the third to the eleventh month of infancy, has been completed. The exception is a study of a small sample of second-born infants that will be completed this year. Data from home observations at three months for the main longitudinal sample has reached the stage of dimensional analysis, and subgroup comparisons are being made for such factors as sex of child and age of mother.

Although the major interest of this section is in current analysis of the most recent longitudinal data, Sandra Jones has published a paper using data from one of the preparatory studies carried out between 1962 and 1963. The data consist of home observations of mother-infant interaction covering the period from the first to the ninth week, and provide a fine-grain recording of interaction sequences between mothers and infants for sustained periods. Sandra Jones' paper used this rich source of information to test, among other things, the extent of infant vocalization when the mother was present or absent. The results are disturbing for any theory of language development which assumes that the infant's vocalizations are stimulated, shaped, and practiced primarily through interactions with the mother. It was found that the mother's presence had a suppressive effect and that the infant actually vocalized more when the mother was absent.

Another report from this section also used data from preparatory studies prior to the present longitudinal program. Howard Moss and Kenneth Robson reported a detailed study of the relationship between the distribution of infant states and visual behavior. An important hypothesis emerged, namely that the male infant's endogenous characteristics, as shown in his distribution of states, may be most relevant to his visual attention, whereas social learning contributes more heavily to the visual performance of females. Findings from this paper may play an important role in understanding the relations between congenital characteristics, as seen in the infant's pattern of states, and the manner in which the first stages of the socialization process begin to develop in early infancy.

Section on Infant Development

This section came under the direction of a new chief in December. After contacting all universities providing graduate training in early infancy, we were fortunate in locating Raymond Yang at Cornell University, whose early graduate training at the University of Hawaii had included extensive work with newborns. He has become familiar with data gathering operations that were completed before he arrived, and has assumed the direction of analyses that were already well underway. It has been very helpful that two of the three nurses who gathered the data are still in the section, and Thomas Douthitt, the former section chief, is readily available for consultation, having transferred to another laboratory of the intramural research program.

The section is well into analyses of observer agreement and test-retest stability. These analyses are especially difficult and complex because the studies of the newborns extended over a three-year period, making it necessary, in the case of each variable involving judgment, to check for drift over time in the nurses' ratings, for differences in general

level of each nurse's ratings, as well as for rank-order agreement with other nurses, at any given stage of the study.

A monograph on a preparatory study will appear this year, and the findings have been presented by Richard Bell and Raymond Yang, and other members of our branch, at the recent meeting of the Society for Research in Child Development. Although our staff had only reported on a preparatory study designed to test procedures and provide a preview of relations that might be found in the main longitudinal study, the report received considerable attention at the meeting. This was one of the few follow-ups from the newborn period that could clearly demonstrate relations to later behavior. It is of some note that discussants and others at the meeting commented on the methodological precision that had been achieved in this study, despite the difficulties of relating very different behaviors in the early and later periods.

Only one segment of the cross-stage relations reported in the monograph was presented at the meeting just mentioned, that dealing with the association of high sensitivity to tactile stimuli in the newborn period with lack of assertive, goal-oriented behavior in response to barriers in the preschool period. One other segment of the findings will be reported this fall at the convention of the American Psychological Association, by Richard Bell, Mary Waldrop and Charles Halverson. In this case, the association of low respiration rates in the newborn period with later advanced verbal communication skills will be reported. This and other findings from the study generally showed what might be called a longitudinal inversion of intensity, in that high magnitude behavior in the newborn period (rapid respiration, tactile sensitivity, and vigorous protest reactions to interruption of sucking) were associated with lethargic behavior in the preschool period (lack of interest and participation, lack of assertiveness, and a lower level of verbal communication).

A more complete understanding of the cross-stage relationship between tactile sensitivity and barrier behavior was brought out in another segment of the preparatory longitudinal study reported by Charles Halverson and Mary Waldrop at the SRCD meeting. In our preschool studies we had speculated that barrier behavior might involve something more than assertiveness. The follow-up to the school-age period, carried out by the Section on Child Behavior, showed that vigorous and goal-oriented behavior in the preschool period was related to later verbal intelligence and use of fantasy in the early school-age period, as well as to social ease, lack of fearfulness, and more adequate coping with a strange new situation. While the main longitudinal study was not intended to go beyond the early preschool period, the extension of this preparatory study was invaluable in throwing light on the meaning of preschool behaviors from the vantage point of a later stage of development in which cognitive capabilities are much better differentiated and identifiable. These findings are of particular interest because cognition is currently one of the most active areas in developmental research.

In the Branch symposium to be held at the coming American Psychological Association meeting, on the relations between congenital characteristics

and verbal communication, Charles Halverson and Mary Waldrop will report an additional finding from the 7-1/2 year follow-up, the relation of attention in play to earlier preschool verbal communication.

Although the Section on Child Behavior has been able to devote considerable time in the early part of this year to analyzing results from the preparatory studies, the major commitment of the section is to the ongoing data gathering at the preschool phase in the main longitudinal study, that will continue until 1973. This activity has become increasingly demanding toward the end of this year. This section is now the largest in the branch, since positions were transferred from others that had completed data gathering. Nonetheless, the staff of nine is heavily taxed to maintain its demanding and intricate observation schedule. In addition, the staff faces some very difficult practical problems incident to transporting children from practically all points in the greater metropolitan area. The most pressing practical problem, however, is that of age-density, the fact that more children are coming of age in the present year than can be accomodated in the nursery school. This problem has required the scheduling of one group of cases after another, without an inter-session interval, in order to study children before they are outside the age range set for the preschool follow-up. It is a tribute to the research commitment of the Section on Child Behavior that its members have sacrificed needed vacations for many months to come, and have assumed very heavy work-loads in order to solve this problem that is so critical to the success of the entire longitudinal study.

Summary

While it has been engaged in studies of the human life cycle, this branch has developed a cycle of its own. Three of its four research teams are now engaged in the kinds of data analysis that were carried out several years ago in preparatory studies. They are currently checking the quality of their data and studying relations within each of the stages with which they are concerned. When they are satisfied that what has been sorted out is meaningful, they will turn to the most important question of all, "Can orderly sequences be found in the succession of events through which marriages, infants, and young children pass?" Our scientists have gone through all of this before, in several years of preparatory studies, but now, in the main longitudinal study, they address the question with some knowledge of measures which should be most valuable, the kinds of individuals that are most likely to appear, and with even some glimpses of patterns that may appear between stages. Because of these prior glimpses, excitement and working hypotheses have replaced the hopes and blind problings that existed in this same phase of the cycle in the preliminary studies. The capability of checking these hypotheses against reality has also changed in this cycle, since our current use of larger samples strengthens the chances of identifying meaningful patterns of family and child development.

Annual Report of the Laboratory of Clinical Psychobiology

National Institute of Mental Health

Frederick Snyder, M.D., Chief

July 1, 1970 -- June 30, 1971

The predicament of this organizational unit is awkward to describe. Comparing it to an iceberg floating in the Gulf Stream would not be entirely accurate, since it never has approached that size or solidity. Rather it is more like that of a sapling stunted from lack of nourishment, yet continuing to send out hopeful shoots in new directions.

Over the four inclement years of its existence the heart of the LCP program has been a clinical research and treatment unit devoted to intensive studies of psychobiological relationships, most particularly those between sleep derangements and mental illness. From the first that unit has produced a small but select harvest including: (1) the initial work on muscle enzyme changes in relation to psychosis by Dr. Herbert Meltzer; (2) the most extensive and thorough studies so far accomplished on the natural history of sleep disorders in depression and schizophrenia; (2) an impressive series of studies on the effects of various drugs on sleep; and (4) the pioneering work of Dr. Richard Wyatt on the biochemistry of human sleep for which he received this year's Bennett Clinical Science Research Award of the Society for Biological Psychiatry. In the absence of an adequate corps of permanent researchers devoted to these efforts, however, it was only by good fortune that the few individuals temporarily staffing the unit during its first years happened to include those with the special dedication and interests to carry through such laborious researches. With further staff reductions and less good fortune, over the past few years that clinical program has reached a point of diminishing returns and will be terminated. It remains to be seen whether LCP can remain at all 'clinical' without the professional staff which went with that inpatient unit, but it is hoped we shall be able to carry forward a small program of outpatient research on sleep disorders.

The new shoots which have sprouted during the past year are: (1) studies on the psychobiology of aggression by Dr. Burr Eichelman, and (2) studies of waking psychophysiology in patients and normal volunteers by Dr. Redford Williams. Both of these men have shown admirable initiative and energy in getting their programs well started without adequate facilities or personnel support. At the same time

our own deficiency of researchers has been partially compensated by collaboration with the staff of the Walter Reed Army Institute of Research, particularly Dr. Willam C. Orr. That collaboration involves work on human sleep and waking psychophysiology here as well as studies of the effects of stress on monkey sleep at the Army Institute of Research.

Dr. Williams and Dr. Eichelman were both selected for their present assignments here five years ago, when planning for the development of the future laboratory was expansive and optimistic. In the mean time each has become involved and established in areas rather distant from our previous rather narrow focus on sleep research, but no less relevant to the general field of psychobiology.

From his Ph.D. work at the University of Chicago, Dr. Eichelman brings us a comprehensive awareness of the current status of research on aggression in animals. Utilizing several simple but well standardized behavioral tests he has undertaken a wide ranging plan of study encompassing: (a) genetic differences, (b) experimental manipulations such as hunger, stress, sleep deprivation and REM deprivation, (c) pharmacological interventions by means of intracistenal and topical cannulae, (d) specific brain lesions and sensory deficits. Although Dr. Eichelman had a very ambitious program in mind when he arrived, his skills and interests have elicited numerous opportunities for collaboration throughout NIH leading to numerous unexpected and exciting turns. One of the most recent has been the five-fold increase in shock-induced fighting after cistenal injection of 6-hydroxydopamine. Another has been that, while olfactory bulbectomy blinding or deafness have no effect on shock-induced aggression, removal of rat vibrissae dramatically decreases fighting! A human equivalent would be of profound geopolitical significance.

Dr. Redford Williams, Jr., brings us a background in internal medicine from Yale and a passionate interest in psychophysiology and psychosomatics. While still in residency he carried out studies demonstrating consistent rises in diastolic blood pressure during interviews involving interpersonal interaction and outward direction of attention. Since coming here last year he has pursued the same theme in terms of another physiological index, forearm blood flow, while working toward applying an entire battery of psychophysiological measures and further defining the critical psychological variables involved. Concurrently he has made a very promising beginning at the intensive study of day to day psychophysiological changes in some of our psychiatric patients. He and Dr. Eichelman together are also exploring behavioral influences upon blood pressure variations in the rat.

One other innovation stems from a happy collaboration with Dr. William Orr of the Army Institute of Research. He and his colleagues there have developed very sophisticated techniques for detecting regularly recurring rhythms during waking both in physiological indices and in behavioral performance, rhythms which appear to be effected by sleep deprivation as well as by neuropharmacological agents. To us the most intriguing aspect is the finding of a very consistent 90 minute cycle in waking comparable to the 90 minute REM cycle in sleep. Since we have long wondered whether the REM cycle might actually be a manifestation of continuous biological rhythm, we have been delighted by his willingness to combine his approach with the sleep research techniques familiar to us. One contemplated study will determine whether the 90 minute waking cycle is accentuated after several nights of deprivation of REM sleep by awakenings. In the same vein we shall see whether the waking cycle is still present in patients receiving MAOI inhibitors, which totally eliminate REM sleep over extended intervals.

Although Dr. Wyatt left LCP two years ago to establish his own sleep research program within the Laboratory of Clinical Psychopharmacology, we continue to profit from fruitful collaboration with him in studies concerned with the biochemistry of human sleep. One study with him and members of the Laboratory of Clinical Science during the past year initiated an approach not previously used in human sleep research involving brief intravenous infusions of drugs while patients' sleep is monitored. In the work so far completed L-Dopa infusions have been found to have acute effects on the REM sleep mechanism, delaying its onset and inhibiting its continuation once begun.

Another pharmacological study completed by Dr. J. Christian Gillin and Leonard S. Jacobs demonstrated a REM suppressive effect of the glucocorticoid, prednisone, and may have broad clinical as well as biochemical implications. If elevations of natural corticosteroids have similar effects under conditions of stress, then we are in a position to understand some, and perhaps all of the abnormalities of sleep found associated with mental illness. We have described REM suppression as the characteristic alteration in sleep in acute schizophrenic and depressive episodes and have new evidence to the same effect in acute manic episodes, all situations in which elevations of corticosteroid levels are also found. If such conditions persist over long intervals, probably months in duration, resulting REM deprivation could be expected to produce the more striking abnormalities of sleep found in psychotic depressives, i.e., abbreviated REM latencies at sleep onset, hyperactive REM eye movements, and shortened cycle intervals.

The above relationships remain hypothetical so long as we have never been in the position to directly observe the above described transition between acute REM suppression and the manifestations found in psychotic depression. If the reasoning is correct, however, it should be possible to produce an experimental model of the same sequence. This is the intent of studies just begun at the Army Institute of Research in collaboration with Dr's William Orr and Joseph Sharp. Monitoring sleep EEG patterns by implanted electrodes and urinary steroid outputs in chair acclimated Rhesus monkeys, we shall look for effects upon sleep of both acute and chronic stress produced by adversive conditioning. If it does prove possible by such means to produce the alterations of REM sleep seen in psychotic depression, then the way will be open for seeking correlated neurochemical and neurophysiological abnormalities by methods not possible in human subjects. Thus, although the mission of this laboratory was originally conceived in terms of parallel and interacting studies of clinical problems and animal experimentation, circumstances dictate a tandem alternative. Perhaps we have gone as far as possible in purely descriptive studies of sleep disturbance in mental illness, and now must turn to the animal laboratory for further elucidation of their physiological mechanisms and signficance.

We believe the same is probably true with regard to the broader biological significance of sleep itself and that the best hope for fundamental understanding lies in pursuit of its widely variable manifestations in different animal forms. Our lengthy labors to develop telemetry techniques for sleep studies in small animals have been rewarded finally during the past year and our studies of prototypical sleep in primitive mammals are well underway. I am most grateful to Tony Bak and Pat Carr of the Laboratory of Neurophysiology as well as to James Bryan and his Section on Technical Development for the indispensable help they have given to that difficult enterprise. It now remains to extend the same approaches to more natural conditions such as our field station at the National Zoo, and to varieties of larger animals not accessible in our laboratory studies. The zoology of sleep remains a vast and almost virgin field of inquiry. We feel extremely privileged to share in its initial exploration and intend to give this area increasing emphasis over the next few years.

Annual Report of the Laboratory of Clinical Science
National Institute of Mental Health
Irwin J. Kopin, M.D., Chief
July 1, 1970 through June 30, 1971

Introduction

The investigations conducted by the Laboratory of Clinical Science aim to elucidate the biochemical, neurophysiological and hormonal processes which determine neuronal function and to explain how drugs, humoral agents and environmental factors may influence the development and function of the nervous system.

The research efforts extend from basic biological research to clinical psychiatry and neurology. The Laboratory is comprised of the Office of the Chief (which includes Units on Clinical Biochemistry, Clinical Pharmacology, Analytical Biochemistry and Psychosomatics) and four Sections: Pharmacology, Medicine, Psychiatry and Experimental Therapeutics. The diversity of interests, talents and approaches to research provide a stimulating atmosphere in which clinical problems can be attacked at a basic level and basic observations are rapidly applied to the clinical situations.

The award of the Nobel Prize for Physiology/Medicine to Dr. Julius Axelrod (Chief, Section on Pharmacology) for works performed in this Laboratory during the past fifteen years was the outstanding event for the year. The magnitude of this achievement dwarfs other major honors earned by our investigators: The Hofheimer Research Award to Drs. Bunney, Murphy and Goodwin and the S. Weir Mitchell Prize for research in neurology to Dr. Ng.

Section on Pharmacology
Julius Axelrod, Chief

The Section on Pharmacology has extended its interests in enzymes concerned with the formation and metabolism of the biogenic amines into the clinical area and, in collaboration with clinical investigators, is studying their occurrence in blood cells and plasma. Basic studies on their appearance in brain during development continue.

A considerable part of the work of the Section has been concerned with a search for enzymes involved in biogenic amine biosynthesis and metabolism in an easily accessible tissue, the blood. Changes in human and animal enzymes under different physiological conditions and in disease can be studied. Dopamine-β-oxidase, an enzyme highly localized in storage granules of sympathetic nerves, was found to be circulating in the plasma of man and other species. The enzyme is elevated in the plasma of man and rat during stress and decreased in rats after destruction of sympathetic nerve terminals with 5-hydroxydopamine. There is no change in plasma dopamine-β-oxidase after removal of the adrenal glands. This suggests that plasma dopamine-β-oxidase arises mainly from the sympathetic nerves. Preliminary studies indicate that plasma dopamine-β-oxidase is decreased in familial dysautomonia.

An assay for the measurement of dopamine-β-oxidase has been developed for the brain. Highest concentration of the enzyme was found in the brain stem and hypothalamus; and lowest, in the corpus striatum. Lesions made in the lateral hypothalamus result in a fall of dopamine-β-oxidase in the ipsilateral areas of the telencephalon.

The development of the noradrenergic neurons has been examined in the fetal and neonatal rat brain. By using the specific neuronal reuptake mechanism for norepinephrine as a marker for the nerve terminals, it has been demonstrated that the noradrenergic nerve terminals first appear four days prior to birth and attain an adult concentration by four weeks after birth. The ability of nerve terminals to store norepinephrine in vesicles develops more slowly. Dopamine-β-hydroxylase, the last enzyme in the synthesis pathway for norepinephrine, is already present seven days prior to birth. During the last week of gestation, it is found primarily in the brain stem where the cell bodies for the noradrenergic neurons are located; but as the nerve terminals grow out, the activity of dopamine-β-hydroxylase increases in other areas of the brain. In the adult, the enzyme has been demonstrated to be tightly bound to the storage vesicles and 70% of the enzyme is located in the nerve terminals.

Destruction of nerve terminals with 6-hydroxydopamine results in a decrease of dopamine-β-oxidase in the sympathetic ganglia and prevents reserpine-induced increases in the activity of dopamine-β-oxidase and tyrosine hydroxylase. A number of drugs including reserpine and 6-hydroxydopamine were shown to increase the activity of tyrosine hydroxylase and dopamine-β-oxidase by a mechanism involving both protein synthesis and neuronal transmission. The induction of these enzymes was blocked by agents which raise the level of norepinephrine, suggesting that catecholamines are involved in the formation of these enzymes.

The following enzymes were found to be present in red blood cells of man and other species: catechol-O-methyltransferase, histamine-N-methyltransferase, methanol-forming enzyme and metionine-activating enzyme. Red blood cell catechol-O-methyltransferase was lower in women (but not men) who have both mania and depression. Patients treated with &-dopa have a decreased red blood cell level of catechol-O-methyltransferase. Histamine-N-methyltransferase is elevated in patients with manic depression or schizophrenia.

Section on Medicine
Irwin J. Kopin, Chief

The Section on Medicine continued studies of the effects of stress on catecholamine-synthesizing enzymes and has developed methods for growing various tissues in organ culture to investigate the biochemical mechanisms of enzyme induction and reinnervation and of synapse formation. The Section has continued to examine the factors which control the synthesis and utilization of catecholamines in the peripheral and central nervous systems and which influence the development and plasticity of the nerve containing these neurohumoral agents.

In the guinea pig vas deferens, chlorpromazine appears to interfere with conversion of dopamine to norepinephrine by inhibiting transport of the precursor into the dopamine-β-hydroxylase-containing vesicles. The finding

that newly synthesized norepinephrine is preferentially released in the vesicle confirms previous findings in the cat spleen. In guinea pig vas deferens, amines which can substitute for norepinephrine at its storage site interfere with noreinephrine synthesis by diminishing hydroxylation of tyrosine. Presumably this is a consequence of inhibition of tyrosine hydroxylase by the released norepinephrine. Acute acceleration of norepinephrine synthesis attending nerve stimulation is not due to an increase in levels of tyrosine hydroxylase, as previously thought from work in another laboratory. This conclusion had been based on indirect evidence that puromycin inhibits the acceleration of catecholamine synthesis; but blockade transport of the precursor amino acid could produce the same effect. Further insight into the mechanism of amine release from sympathetic nerve endings was obtained by the demonstration that dopamine-β-hydroxylase is released during stimulation-induced release of norepinephrine.

In rats stressed by repeated immobilization there is an increase in levels of adrenal tyrosine hydroxylase, dopamine-β-hydroxylase and cyclic-AMP. The increase in cyclic-AMP appears to be confined to the adrenal cortex but is markedly diminished by denervation of the adrenal. The enzymatic changes in the adrenal medulla are dependent in part on the adrenal cortical hormones and in part on the innervation of the adrenal. When mice are made aggressive by isolation and allowed to fight, levels of adrenal tyrosine hydroxylase increase. Mice which are attacked have an increase in this enzyme, but attacking mice which are not resisted do not. The elevation of adrenal tyrosine hydroxylase is not seen in attacked mice treated with phenobarbital.

The successful attempts to grow adrenal medullae, sympathetic ganglia, iris and atrium in organ culture for up to eight days has provided an important tool for examination of the control of enzyme induction, reinnervation and synapse formation. The induction of tyrosine hydroxylase in cultured adrenals depends upon release of the catecholamines rather than on depolarization of the adrenal medullary cell membrane. Nerve fibers from ganglia grown adjacent to irides in organ culture reinnervate the smooth muscle of the iris. Reinnervation appears to depend on nerve growth factor and is markedly diminished when antibody to nerve growth factor is added to the incubation medium. A sensitive radio-immunoassay for nerve growth factor has been developed; this substance has been found in the tissues and is released into organ culture medium. Colchicine and vinblastine, which interfere with neurotubule integrity, block reinnervation. Cycloheximide, which inhibits protein synthesis, also interferes with reinnervation.

Section on Psychiatry
William E. Bunney, Jr., Chief

The Section on Psychiatry proceeded with studies on the biological aspects of affective disorders and initiated a series of investigations of the effects of various psychoactive drugs on amine metabolism as reflected by changes in levels of the amine metabolites in cerebrospinal fluid after blockade of acidic metabolite transport with probenecid. Investigators focused on psychobiological studies of depressive and manic-depressive illness.

A program has been projected over the next few years to continue investigation of the manic phase of the manic-depressive illness and the point of change from depression to mania and from mania to depression. A manic-state rating scale has been developed, and its reliability and validity have been determined during the past year. A regular pattern of change in thought and mood was documented during spontaneous episodes of switches from one state to the other. The events occurring at the time of change from one predominant affective state to another has been operationally defined as the "switch process." Total sleep time was markedly reduced on the day prior to the switch to mania and remained low during the manic period. During the switch to mania, it was further shown that urinary norepinephrine was significantly elevated on the day before and during the manic episode. Similar trends were noted for epinephrine and dopamine. Urinary cyclic-AMP was shown to be increased on the day of the switch from depression to mania.

Brief administration of tricyclic medication was associated in a few patients with rapid switches from depression into a short normal period and then into manic behavior. In bipolar patients with past histories of mania, brief hypomanic episodes were regularly associated with the administration of large doses of ℓ-dopa, the specific metabolic precursor of dopamine and norepinephrine. In a small group of bipolar patients treated with large doses of ℓ-tryptophan, hypomania did not occur. α-Methyl-p-tyrosine, a specific inhibitor of the synthesis of norepinephrine and dopamine, was associated with a rapid transitory switch out of mania in a few patients; it failed to be effective in others. These findings support an important role for the catecholamine neurotransmitters, dopamine and norepinephrine, in the switch process of the manic-depressive illness.

Large doses of ℓ-dopa were administered with and without a peripheral decarboxylase inhibitor, α-methyldopa-hydrazine (MK485) to 23 depressed patients. Only 25% of the total group showed a consistent improvement in depression on ℓ-dopa. Before treatment, all of the respondents were retarded. An intensification of existing psychotic symptoms with ℓ-dopa was noted in the psychotically depressed patients who did not show a therapeutic response. In a further attempt to test the catecholamine hypothesis, α-methyl-p-tyrosine was administered to six depressed patients. Four patients became worse, and two patients showed no change.

Studies of cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, the major breakdown product of serotonin, have revealed a consistent decrease in our group of depressed patients as compared to neurological patients. During the past year, a good deal of effort has been devoted to further validate the probenecid method for the estimation of amine turnover in brains of patients. It has been shown that administration of ℓ-dopa plus MK485 is associated with an increase in the turnover of dopamine and a decrease in the turnover of serotonin. Large doses of ℓ-tryptophan, the metabolic precursor of serotonin, caused a marked elevation in the rate of accumulation of 5-hydroxyindoleacetic acid on probenecid.

Quantitative measures of verbal learning and word association have been obtained in cyclic manic-depressive patients. Learning was markedly impaired during mania compared to both non-manic periods in the same patients and to the performance of normal controls.

In collaboration with the Section on Pharmacology, the red blood cell catechol-O-methyltransferase activity in patients with primary affective disorders separated into unipolar and bipolar groups has been studied. Women with unipolar illness had the lowest catechol-O-methyltransferase activity; women with bipolar illness had activity intermediate between the unipolar women and the control group. Cellular levels of biogenic amines and amine transport and metabolism in man have also been investigated. Blood platelets contain amines and amine-related enzymes and thus provide a model system for studies of the effects of psychoactive drugs at the cellular level. ℓ-Dopa and ℓ-tryptophan administration have been found to affect serotonin levels in platelets from patients receiving these drugs. ℓ-Tryptophan increased serotonin content, and ℓ-dopa decreased it.

Section on Experimental Therapeutics
Thomas N. Chase, Chief

The Section on Experimental Therapeutics has investigated amine metabolism in spontaneous and drug-induced motor disorders and examined the possible ways in which ℓ-dopa could produce its therapeutic and toxic effects. The Section has attempted to elucidate the role of central monoamines in the pathogenesis of neurologic disease and to examine the mechanisms by which drugs act on the central nervous system.

During the past year it has been found that the probenecid-induced rise in cerebrospinal fluid levels of homovanillic acid, a major metabolite of dopamine, and of 5-hdyroxyindoleacetic acid, the principal product of serotonin degradation, is markedly diminished in patients with idiopathic, postencephalitic or Guamanian parkinsonism. Since probenecid blocks the transport of these phenolic acids from the central nervous system, the results suggest that a reduction of both dopamine and serotonin turnover attends these disorders. Similar but less marked changes have been found in Americans and Guamanians with amyotrophic lateral sclerosis. No alterations in central monoamine turnover could, however, be demonstrated in patients with Huntington's chorea, dystonia musculorum deformans or Down's syndrome. In a group of neurologic patients, haloperidol substantially increased the probenecid-induced accumulation of homovanillic acid but not of 5-hydroxyindoleacetic acid. This finding is consistent with results of animal studies showing that haloperidol and related psychotherapeutic agents accelerate central dopamine turnover. Cerebrospinal fluid studies in patients receiving ℓ-dopa suggest that the administration of ℓ-dopa releases both serotonin and norepinephrine from central stores.

A single-blind cross-over study in 14 parkinsonian patients has compared biochemical and clinical effects of ℓ-dopa alone and in combination with α-methyldopa-hydrazine, an extracerebral inhibitor of amino acid decarboxylase. Use of the decarboxylase inhibitor reduced the optimal therapeutic dose of ℓ-dopa-induced emesis, thus permitting a marked acceleration of the rate in which the ℓ-dopa dose could be increased to therapeutic levels. Investigations of the therapeutic efficacy of ℓ-dopa in brain disorders other than idiopathic Parkinson's disease continue. ℓ-Dopa substantially improved extrapyramidal function in eight Guamaniams with Parkinsonism-dementia but did not ameliorate dementia. A trial of ℓ-dopa in ten amyotrophic lateral sclerosis patients failed, however, to improve motor function.

5-Hydroxytryptophan, the immediate precursor of serotonin, increased akinesia and rigidity in seven parkinsonian patients. This result suggests that elevated brain serotonin concentrations may have an effect opposite to that of dopamine in parkinsonian patients; on the other hand, since 5-hydroxytryptophan competes with &-dopa for uptake, metabolism and storage, it is perhaps more likely that the clinical response to this agent is a consequence of reduced dopamine stores at extrapyramidal centers. Preclinical studies indicate that a portion of exogenously administered &-dopa may enter central serotonergic terminals, undergo decarboxylation to the amine and subsequently be liberated as a substitute central transmitter. This mechanism may contribute to &-dopa's clinical effects in parkinsonian patients and explain why the drug's therapeutic efficacy is independent of the pretreatment severity of the disorder.

Office of the Chief
Irwin J. Kopin, Chief

Unit on Clinical Pharmacology (Julius Axelrod and Irwin J. Kopin, Co-Heads). The metabolic fates of amphetamine and tetrahydrocannabinol (the active constituent of marihuana) have been the major areas of investigation. Delta-9-tetrahydrocannabinol-C^{14} was traced in chronic marihuana users and in subjects who had never used the drug. It was found that part of tetrahydrocannabinol is rapidly metabolized but that a good deal of the compound appears to be stored in the tissues and is released slowly so that it may be detected in the blood for several days after its administration. Chronic users of marihuana metabolize it more rapidly than naïve subjects.

Unit on Analytical Biochemistry (Robert W. Colburn, Head). The Unit has continued to develop methods for screening metabolite excretion patterns in psychiatric patients and to study the disposition of biogenic amines in the synaptosomes obtained from rat brain. The metabolic fate of norepinephrine is altered in these pinched-off nerve endings by drugs such as reserpine and tyramine in the same manner as the drugs alter metabolism of amines in the peripheral adrenergic neurons. Tyramine enhances release of the unchanged amine by permitting its metabolism by monoamine oxidase. Synaptosomes appear to accumulate tetrahydrocannabinol, and the effects of this drug on amines is now being investigated.

Unit on Psychosomatics (Philippe V. Cardon, Head). Investigators have studied the mechanisms by which &-dopa affects the circulatory system. By means of direct recording from sympathetic nerves in cats, it has now been shown that when the animals are pretreated with a peripheral inhibitor of dopa-decarboxylase, administration of &-dopa causes a reduction in sympathetic nerve activity which parallels the reduction in blood pressure and heart rate.

The circulatory effects of delta-9-tetrahydrocannabinol on ten marihuana users have been studied. As reported by others, the active component of marihuana given orally produces psychological effects similar to marihuana. While the psychic effects are present, circulatory effects besides the well-documented tachycardia include loss of or diminution of reflex venoconstriction and possibly some increase of orthostatic arteriolar vasoconstriction.

metabolism was completed in collaboration with Yale University Department of Psychiatry. No effect on glucose tolerance was demonstrable. Insulin, growth hormone, free fatty acids and urinary cyclic-AMP are now being assayed. The preliminary conclusion is that it is unlikely that the heightened adrenal medullary function often observed in depressed patients can account for the impaired glucose tolerance observed in depressed patients.

In collaboration with the Section on Pharmacology, sympathetic ganglionic transmission following treatment of rats with 6-hydroxydopamine was studied. The hypothesis that destruction of neural terminals by this agent would result in transmission block analogous to that seen after postganglionic nerve section could not be confirmed. Apparently normal transmission of preganglionic shocks was observed at all time intervals studied after treatment. Reduction of blood catechol-O-methyltransferase in patients receiving therapeutic quantities of ℓ-dopa was observed in another collaborative project, but the reason for this phenomenon has not been explained. The Unit has also collaborated with the Section on Experimental Therapeutics in several clinical studies of patients with disorders of motility.

Annual Report of the Laboratory of Psychology

National Institute of Mental Health

David Rosenthal, Ph.D., Chief

July 1, 1970 - June 30, 1971

In FY 1971, the decision was made to take the Section on Comparative Behavior and the Unit on Research in Behavioral Systems out of the Laboratory of Psychology and place them in a new laboratory based entirely in Poolesville. Thus, the Laboratory of Psychology will be reduced in size, but the reorganization has administrative advantages. In other respects, the basic aims and directions of the Laboratory remain essentially the same. We still await the time when mental health research will be more fully supported and when new programs in the Laboratory can be implemented.

FY 1971 saw the publication of Dr. Paul Wender's Minimal Brain Dysfunction by Wiley, and Dr. David Rosenthal's Genetics of Psychopathology by McGraw-Hill. Dr. Rosenthal was the recipient of the Ninth Annual Stanley R. Dean Research Award for "basic research accomplishment in the behavioral sciences contributing to our understanding of schizophrenia". He also received the Maryland Psychological Association's Outstanding Contribution Award for 1971.

Unfortunately, the space planned for Dr. Jack Gewirtz's infant study program will probably not be renovated until next year, thus holding up his research. However, the remodeling for the Unit on Somatosensory Processes was completed this year and the Unit is fully operative. The SEL 810 B computer has gone through a thorough debugging period and investigators have been preparing themselves and their research programs to make optimal use of this computer system for "real time" studies that will add a significant dimension to their research. The laboratory's major research accomplishments during this year were achieved in the following areas:

Brain Function and Behavior in Primates:

Cortical Mechanisms in Vision.

Gross and his colleagues at Princeton recently discovered that inferotemporal cells in the monkey have well-defined visual receptive fields, thereby establishing conclusively that the inferotemporal area does receive a specific visual input. Furthermore, the properties of these receptive fields (their large size, extension into the fovea, and bilaterality) are consistent with an earlier conclusion derived from our own anatomical and ablation studies that the visual input to each inferotemporal area stems from the striate cortex of both hemispheres by way of the prestriate cortex and the corpus callosum (the latter being utilized in the case of the crossed inputs). Prompted by this close fit between the new data and the earlier theory, we are collaborating on an experiment to determine whether specific

lesions in this hypothesized cortical pathway will produce predicted alterations in the receptive field properties of inferotemporal cells. As a first step, the property of bilaterality was selected for study. Monkeys were prepared here with either complete unilateral striate removals or transections of the forebrain commissures, and were then studied electrophysiologically by Gross's group. The results have thus far confirmed predictions by showing that in the absence of the left striate cortex, inferotemporal units in both hemispheres have receptive fields that are restricted to the side projecting to the right striate cortex (i.e., the left field for both inferotemporal areas); and also that in the absence of interhemispheric connections, the inferotemporal units of each hemisphere have receptive fields limited to the side projecting to the striate cortex of that particular hemisphere (i.e., the left field in the case of the right inferotemporal area, and the right field in the case of the left). The neural model emerging from these results is that of a system of cortically relayed visual inputs converging onto single units in the inferotemporal area. Additional lesions have now been made in order to test this model in greater detail. The new lesions include bilateral macular striate removals in the attempt to produce "central scotomata" in the receptive fields of inferotemporal units, and unilateral prestriate ablations in the attempt to "disconnect" inferotemporal units from their striate inputs.

Simultaneously with supporting the cortical input model, these results provide an explanation for our finding that massive posterior thalamic lesions failed to interfere with the class of visual functions (namely, pattern and object recognition) known to be dependent on the inferotemporal area. We now know from our anatomical studies that the pulvinar and lateralis posterior nuclei of the thalamus constitute a potential relay for transmitting visual information to the inferotemporal and other extrastriate cortical areas from the superior colliculus, and some investigators have proposed this pathway as an alternative to the cortico-cortical route. In view of our negative findings with posterior thalamic lesions, however, and in view of the new electrophysiological evidence favoring a transcortical pathway as the mechanism for an object-recognition system, it appears that whatever visual information reaches the cortex via the colliculus-posterior thalamic projection must be serving some other class of visual functions. Our tentative hypothesis is that this projection plays some role in spatial vision, for the following reasons: First, studies by others on non-primate mammals have implicated the superior colliculus in visual spatial orientation; second, results from a recent study in our laboratory imply a similar function for the prestriate/posterior parietal cortex in the monkey; and third, the major projection from the pulvinar and lateralis posterior nuclei in the monkey is to this prestriate/posterior parietal area rather than to the inferotemporal region. Piecing these findings together, we have suggested that just as the geniculostriate-prestriate-inferotemporal pathway seems to be concerned mainly with such foveal visual functions as pattern and object recognition, the superior colliculus-posterior thalamus-cortical pathway may be concerned chiefly with such extrafoveal visual functions as the perception of spatial relations among objects. Studies to test this conception are in progress; they involve an examination of the effects of pulvinar and lateralis posterior lesions in the monkey on the same visual spatial tasks (such as

landmark discrimination learning) that elicited impairment in animals with prestriate/posterior parietal lesions.

The evidence cited above in support of a transcortical pathway from striate through prestriate to inferotemporal cortex favors a "serial processing" model for object vision. This raises the question of whether or not such a model can be extended beyond the visual system to encompass stimulus-reward associative learning. Translated into functional anatomical terms, the question is whether visual objects might gain motivational and emotional significance through an interaction between the inferotemporal cortex and the limbic system. The three major telencephalic outputs from the inferotemporal area are (a) to the orbital frontal cortex, (b) to the temporal pole and amygdala, and (c) to the fusiform-hippocampal gyrus and hippocampus. As a start toward investigating the possible role of these inferotemporal-limbic pathways in visual associative learning, three groups of animals, each with damage to a different one of the three limbic structures, were compared with unoperated controls in object reversal learning. This task was chosen because of its known sensitivity to associative learning processes. The results indicated that whereas the hippocampus, and by implication, pathway (c) is probably not involved in visual associative learning, both of the other limbic structures, and by implication, both of the other pathways, are intimately involved. Furthermore, these two pathways (a and b) probably serve different functions in visual learning, since the two lesions (orbital frontal and temporal pole plus amygdala) yielded a double dissociation of deficits. Specifically, the frontal group was more impaired in extinguishing or abandoning old habits, while the temporal group was more impaired in establishing new ones. Future work will be directed toward the functional anatomical problem of whether the presumed interaction between the inferotemporal and anterior limbic areas is mediated by cortico-cortical connections.

Frontal Cortical Mechanisms in Spatially-Directed Responding.

Although lateral prefrontal lesions in the monkey are known to produce impairments on spatial delayed response and spatial delayed alternation, there has always been some question as to whether the delay, the spatial features, or a combination of the two is the critical factor giving rise to the impairments. Accordingly, the effects of several different lateral frontal lesions were compared on spatial tasks, one which involved delays (delayed alternation) and one which did not (a conditional position response test). The findings indicated the existence of two functionally distinct subdivisions within the dorsolateral prefrontal cortex: one in the principal sulcus, damage to which was responsible for impaired performance on the spatial task with delay; and the other in the arcuate sulcus, removal of which was responsible for impaired performance on the spatial task without delay. The dissociation of deficits following lesions in the principal sulcus on these two spatial tasks indicated that spatial factors alone were insufficient to account for the classical delayed-alternation deficit after principalis lesions and pointed instead to the importance of the delay. However, there was evidence to indicate that mnemonic factors alone also cannot account for this characteristic prefrontal deficit. These considerations led to the hypothesis that it was only when both factors - spatial responses and delays - were present together in a task, as they are in delayed alternation, that a lesion

of the principal sulcus produces a severe disability. Two additional experiments which test this proposal have recently been completed. The first experiment compared the effects of arcuate and dorsolateral lesions on two spatial tasks not studied previously in this context. These tasks (delayed response and place reversal) each contain both spatial and mnemonic factors. The second experiment compared the effects of focal lesions in a new set of monkeys on a task, go no-go alternation, which contained only the mnemonic but not the spatial requirement. The results demonstrated that lesions of the principal sulcus produce marked impairments only when both factors are present. When only the mnemonic feature is present in a test, as in go no-go alternation, or only the spatial factor, as in the conditional position response studied previously, the tests are no longer sensitive to the disorder produced by removal of the principal sulcus but rather to that produced by ablation of the arcuate cortex. These studies of small focal lesions on a variety of spatial and nonspatial tests have revealed an unanticipated specialization within the dorsolateral region and thus dispelled the prevalent conception of a unitary dorsolateral mechanism. They have also provided insight into the nature of the classical deficit in terms of a loss in immediate memory for spatial information. The notion of a modality-specific memory loss produced by prefrontal lesions in the tradition of Jacobsen's formulations earlier in the century is not incompatible with the more recent proposal of "gnostic" areas by Konorski. Until now and in general, however, the significance of memory in prefrontal deficits had been largely ignored.

Cerebral mechanisms in compensation of functional loss after brain injury.

While the dorsolateral cortex in the adult is intriguing because of the profound and selective deficits which result from its removal, in the infant, dorsolateral cortex is intriguing precisely because no deficits appear to develop after it is removed. Also, whereas in the adult we are confronted with the task of defining the nature of the functions mediated by the dorsolateral cortex itself, in the infant, the problem is rather to comprehend the workings of that part of the brain which presumably is responsible for taking over the functions of the damaged dorsolateral cortex. Our initial investigations were directed toward determining if the orbital prefrontal cortex was involved in the compensatory readjustment. Although the evidence obtained could be interpreted as support for the idea, a more compelling interpretation emerged. This new proposal suggested that whereas the functions of the dorsolateral cortex could be compensated, those of the orbital cortex could not. Several experiments directed toward examining this notion have been completed and with positive support for the differential sparing notion. These studies, while very important, were not, however, crucial. This year we have completed analysis of a critical test of the hypothesis. Infant-operated monkeys with dorsolateral lesions were compared with infant-operated monkeys with orbital lesions, as well as with unoperated and late-operated controls. The prediction that dorsolateral monkeys would perform as well as normals on the test battery while orbital monkeys would be selectively impaired was confirmed. The findings from this and previous research leads to the conclusion that orbital prefrontal cortex develops earlier in ontogeny than the dorsolateral cortex.

Given the evidence for the selective sparing hypothesis, two further questions have evolved. One has to do with the age at surgery and the other with the age at testing. An experiment is underway to determine whether sparing of orbital function could perhaps be obtained if the orbital prefrontal area were removed at still earlier ages. Accordingly, the effects on subsequent performance of orbital lesions made at 1 week, 1 month, and 2 months of age are being compared. If no evidence of compensation is found, it will be concluded that development of orbital cortex is completed prenatally. The other question, already answered, is whether orbital deficits can eventually be repaired at later stages of development than those at which the primary loss was determined. It turns out that when early-operated monkeys with orbital lesions are retested at 24 months of age, there is evidence of restitution. This must indicate that the neural substrate for compensation reaches its full potential sometime between the earlier testing age 12-15 months and 24 months of age. Since the available evidence in lesioned monkeys indicates that orbital cortex develops sooner than dorsolateral cortex, it seems reasonable to suppose that the dorsolateral cortex does not complete its full development until around two years of age. This analysis emphasizes the essential developmental aspect of compensatory mechanisms in early-operated monkeys and indicates that recovery is related to the relative maturity of functionally-related structures remaining after surgery. If these areas are fully "committed" as in the adult, little recovery would be expected. If these areas are not fully "committed" as may be the case in the developing organism then recovery might be expected, although it would not necessarily be evident until the areas in question have reached their full development. The notion of "commitment" provides a clue to the mystery of the plasticity problem, i.e., the differential capacity for recovery in infants and adults following the same cortical injury. All of the current developmental work in this laboratory is being directed toward unraveling this problem.

Cortico-subcortical mechanisms in the regulation of behavior.

Our earlier work had demonstrated with anatomical procedures that efferent projections of the prefrontal cortex terminate in a topographic arrangement on subcortical structures. We have now demonstrated in further anatomical studies that each of these sectors in the head of the caudate sends fibers selectively to different parts of the globus pallidus and the substantia nigra. In the globus pallidus, the fibers from the anterodorsal caudate take a lateral position, while those from the ventrolateral caudate take a medial position. It is known that each of these parts of the pallidum, in turn, projects to different structures; the lateral part to the subthalamus, the medial part to the thalamus. Thus, there are at least two systems, one consisting of dorsclateral frontal cortex, anterodorsal caudate, lateral pallidum, and subthalamic nucleus; the other, consisting of orbital frontal cortex, ventrolateral caudate, and thalamus. The question arises as to whether or not each of these two well-defined systems subserves different behavior. It had been known for some time that the functions of the cortical components of the two systems are clearly dissociable and some of our earlier work demonstrated that the functions of parts of the head of the caudate nucleus were also dissociable on a basis determined by their relationships with the frontal cortex. That is to say, those functions which are differentially affected by dorsolateral and orbital frontal cortical lesions are likewise

differentially affected by lesions in the anterodorsal and ventrolateral parts of the caudate, the projection areas of the respective cortical areas.

The concern of more recent studies has been whether or not the dissociation of function in the subcortical projections of the two frontal systems is maintained beyond the pallidum. The centrum medianum of the thalamus receives projections from that part of the pallidum related to the orbital frontal system (the medial pallidum), and not from that part of the pallidum related to the dorsolateral system (the lateral pallidum). It would be expected, therefore, that the centrum medianum would subserve functions of the orbital and not of the dorsolateral system. A study designed to test this hypothesis demonstrated that the centrum medianum does not subserve functions, at least of those tested, of either system; monkeys with extensive lesions in the centrum medianum are not impaired on the usual tests of frontal-lobe function. This finding indicates that the functions of the centrum medianum, like the dorsomedial nucleus, another medial thalamic nucleus uninvolved in these tests, is not determined by its afferent anatomical relationships with the frontal-caudate-pallidal system. A positive finding from this study, that monkeys with centrum medianum lesions had higher than normal thresholds for detecting pain, demonstrated that the centrum medianum in the monkey, as in a variety of other animals including man, is involved in an animal's reaction to pain. This is consistent with the notion that the centrum medianum is related to the limbic division (medial-orbital) of the frontal cortex since lesions in such cortex also alter the reactivity to painful stimuli.

Our earlier anatomical studies had also demonstrated that in addition to projecting differentially to the caudate nucleus, the dorsolateral and the orbital frontal cortex projects directly and differentially to the lateral and the medial hypothalamus, respectively. This is consistent with the findings of others that there exists an intimate anatomical relationship between the frontal cortex, particularly the orbital (limbic) part, and the hypothalamus. Furthermore, many studies in a variety of animals have demonstrated similarities in the physiology and behavior subserved by these structures, leading to the notion that in many respects the frontal cortex may be considered a projection area of the hypothalamus. It has been demonstrated in many situations that the hypothalamus is highly differentiated anatomically and that different areas subserve different functions. There is agreement that the functions of the lateral hypothalamus are different from the medial, and also that those functions of the anterior hypothalamus are different from the posterior. In general, however, these differences have been shown mainly for motivational and emotional mechanisms, and very rarely have they been related to cognitive functions. Furthermore, the differences in behavior which have been shown do not easily lend themselves to explanations in terms of the differential anatomical projections from the dorsolateral and orbital divisions of the frontal cortex which we had demonstrated in our earlier studies. Accordingly studies have been undertaken to examine whether or not cognitive functions are affected by hypothalamic lesions, and whether or not the functions of the different areas of the hypothalamus may be dissociated on the basis of their anatomical connections with the dorsolateral and the orbital frontal cortex respectively. In different groups of monkeys lesions have been selectively placed in the anterior, lateral, and medial hypothalamus and are

being tested on visual pattern discrimination, spatial delayed alternation, and object reversal, tests which distinguish between the effects of dorsolateral and orbital frontal lesions. Preliminary results suggest that all operated animals are impaired on all tests. If this is confirmed in additional animals, it will have to be concluded that the differential projection from parts of the frontal cortex are irrelevant for the behavior examined in these tests and that the hypothalamus enters into cognitive behavior nonspecifically, probably contributing a general motivational factor.

Cerebral mechanisms in the regulation of appetitive behavior and social interactions.

A. Brain stimulation and the regulation of thirst. The experiments in this study were completed last year. This year histological analysis has been completed and the findings prepared for publication. The study involved four monkeys in which a total of 80 chronic electrodes had been implanted in brain areas where electrical stimulation elicits drinking. The effect of stimulation in these areas was examined with respect to various degrees of thirst motivation and the reliability of the effects over length of time of stimulation. The major findings are that (1) Some animals drink to brain stimulation, others do not, even though the same brain structures are stimulated. (2) In those animals that drink to stimulation, the volume of brain system mediating the response increased during the six weeks of stimulation for drinking points; i.e. a greater proportion of sites gave rise to the response as the exploration for sites proceeded. In non-drinkers the anatomical system from which drinking could be elicited became smaller. (3) Within animals, the relationship between self-stimulation and drinking elicited from selected points was consistent from point to point, but the kind of relationship differed for the two animals which were studied in this regard. The interpretation being placed on these data is that activity in at least some cells in the hypothalamus motivates behavior only in a general sense until physiological and/or environmental conditions are such as to shape a specific behavior pattern. Furthermore, these cells can be committed to other functions should the condition change.

B. Social and emotional behavior in brain-lesioned infant monkeys. The experimental work in this study was completed last year. In this year analysis of data has been completed and the conclusions published. More than 50 different behaviors were studied by time-lapse video recordings in thirteen one-year old monkeys in which either dorsolateral or orbital prefrontal cortex had been removed from their brains when they were fifty days old. They were observed first in their home cages in stable living groups which had existed for at least 6 1/2 months and then again immediately after they had been separated from one another. The major results indicated that monkeys with orbital lesions differed from unoperated controls in more ways than did the dorsolateral monkeys: when they were in groups, the animals with orbital lesions slept more and were more sedentary even when awake; when they were living singly, by contrast, they became hyperactive and spent most of their time in locomotion. These findings lend support to the notion, derived from studies of cognitive behavior in infant-operated monkeys, that functions of the orbital frontal cortex, unlike those of the dorsolateral cortex, are not

spared following brain damage in infancy. Further, the nature of the behavior exhibited by impaired monkeys led to the suggestion that the orbital cortex may play an important role in modulating arousal mechanisms in the infant and adult monkey alike.

Somatosensory Processes

Our recent experimentation has focused on the roles of the lemniscal vs. the extra-lemniscal somatosensory pathways, as indicated by the effects of removing the cortical projection areas of the former pathway, which are primarily the postcentral gyrus (SI) contralateral to the hand tested, and secondarily, the parietal operculum (SII). The lemniscal system is of particular interest because electrophysiological studies by others have shown that it contains the narrowly-tuned afferent cells, which have been considered to be essential for fine sensory discrimination; in contrast, the extra-lemniscal system is for the most part made up of broadly-tuned units, which have been thought to be capable of mediating only the grosser forms of somatic sensation (perhaps mainly pain).

The first experiment compared the effects of four equal-sized adjacent lesions of the sensorimotor hand representation in the central gyri -- anterior precentral, posterior precentral, anterior postcentral, and posterior postcentral. The behavioral effects obtained on a battery of somatosensory discriminations confirmed (more clearly than in previous experiments by others) the notion that the anterior postcentral gyrus lesions were by far the most deleterious. Both types of precentral ablations were completely without effect, an unexpected result which demonstrated a sharp functional boundary between sensory and motor cortical areas.

The posterior postcentral removals impaired performance only on difficult shape discriminations. This experiment will also be useful in establishing the precise topography of the projection from the principal somatosensory thalamic nucleus to the central gyri, by means of a comparison of the loci of retrograde degeneration in the thalamus produced by each of the four cortical removals.

On the basis of the behavioral findings, the effective lesion (the anterior postcentral and area) was subdivided into two: the cortex of the posterior bank of the central sulcus (roughly corresponding to cytoarchitectural area 3) vs. the tissue on the crown of the gyrus (roughly corresponding to area 1). It was found that lesions of "area 3" were mainly responsible for the deficit, although lesions of "area 1" had slight effects. Since it is known that area 3 sends cortico-cortical fibers to area 1, the question arose as to whether the latter area was functionally denervated by removal of the former. To answer this question and to verify the distinctness of the two lesions, monkeys with each type of removal were studied electophysiologically just before sacrifice, using the technique of microelectrode mapping of the remaining anterior postcentral cortex. Each area appeared to be grossly normal in the absence of the other, a finding which supports the view that the behavioral deficits observed after these respective removals were independent.

The nature of the deficit after the anterior postcentral lesion was

explored further by supplementary behavioral tests. Despite the severe deficit found on the battery of somatosensory discrimination tests, monkeys with this lesion surprisingly retained, or recovered, normal sensitivity to punctate tactual stimuli. These tests were done with a series of modified von Frey hairs applied to the skin of the monkey's hand; thresholds were repeatedly determined before and after operation. Two-point discrimination was also tested, and only a slight loss was found. The reason for the operated monkeys' failure to discriminate objects differing grossly in one or another aspect, therefore, cannot be due to a simple sensory hypesthesia of the hand.

A complete lesion of the postcentral gyrus (including leg, arm, and face areas) opposite the hand tested, even when combined with bilateral removal of the parietal operculum, likewise failed to produce consistently more severe effects on tactual sensitivity than those obtained from ablation of the contralateral postcentral hand area alone. The large combined lesion also failed to affect discrimination of fine temperature differences (of the order of 1°C.).

The main problem, then, is to find out the nature of the deficit following anterior postcentral lesions, particularly those of "area 3", the principal projection zone of the lemniscal system. It is clear that there is much more remaining sensibility after such lesions than has generally been supposed. However, it is equally clear that this lesion does cause a severe impairment in discrimination of objects by active palpation. We have also found deficits in cortical reflexes (placing and hopping) and habitual abnormal postures of the upper limb, although it must be emphasized that monkeys with lesions of "area 3" or "areas 3 and 1" do not appear to be deficient in the kind of active palpation required by the object discrimination tasks, or in reaching accurately for food morsels.

The findings described, although confirmatory of classical notions in certain ways, obviously indicate the need for attempting a re-definition of the lemniscal contribution to somatosensory discrimination performance, since the losses uncovered do not fit the hypothesis that there is a simple hypesthesia at the basis of these losses. The problem of cortical mechanisms of temperature discrimination must also be pursued further. Preliminary results suggest that the hemisphere ipsilateral to the hand tested may play an important role, thus pointing to an extra-lemniscal contribution, and by implication, to a more important function of the multisynaptic "spinothalamic" tract in the higher levels of this form of sensation than has heretofore been realized.

Schizophrenia

We are heavily engaged in analyzing the vast amount of data we have been collecting in Denmark and Israel. In Denmark we find that the morbidity risk for schizophrenia in our adoptee population is probably lower than any of the rates reported in eight population studies previously carried out in Scandinavia. The data also suggest that adopted away offspring of schizophrenics have a lower rate of hospitalized schizophrenia than the rates reported for schizophrenics' offspring generally in previous studies. We shall explore several possible explanations of these findings, including the possibility that separation from schizophrenic relatives protects one from hospitalization for schizophrenia. We are engaged in testing the concept of a

"schizophrenic spectrum of disorders", but cannot as yet draw any hard conclusions on this crucial question in psychiatric diagnosis and in our understanding of abnormal behaviors. In our quest to identify behavioral characteristics of gene-carriers, we find that people who have a schizophrenic biological parent are less likely to emigrate than matched controls who do not have a schizophrenic biological parent. The controls emigrate at a rate similar to that of the Danish population at large. This failure to emigrate suggests that our gene carriers have no get up and go, lack a sense of and taste for adventure and change, or are not able to organize the planning required for successful emigration. Index cases were also more likely than controls to state that, when they found out that they were adopted, they had fantasies of what their real parents were like, but in reality they made no effort to find out who their biological parents were or what they were like, but seemed content to hold on to their fantasies.

In Israel, the psychologist who examined the children in a clinical interview, and who was blind with respect to their index or control status, was able to distinguish the index and control subjects on a considerable number of traits which he refers to as: mental activity, group activity, concentration, energy, initiative, involvement, peer-relations, suspicion toward peers, feelings of not belonging, oral habits, humor, lisping, fluency of speech and pre-schizophrenic trends. Of the 100 children who were examined (ages 8 to 14) two have since "broken down". Both were index cases, one from the kibbutz, one from town. A third is said to be "on the verge of a breakdown". This child is also an index case and is a kibbutz child. Fortunately, we received support to follow and examine these unique subjects again over an additional three year period. The analysis of the large amount of data collected in Israel is continuing as rapidly as possible.

We had found previously that chronic and acute schizophrenics do not exhibit a generalized deficit in the responsivity of the autonomic nervous system as has sometimes been thought, but show such a deficit selectively, particularly in response to meaningful stimuli and to "stressors" such as task performance. In a large correlational analysis of the autonomic data with behavioral and biochemical data collected by other investigators on a group of monozygotic twins, most of whom are discordant for schizophrenia, we have extended this finding by showing that this specific deficit in autonomic responsivity is correlated with the severity of symptomatology and behavioral disturbance in schizophrenics and to low ego strength in controls. Further analyses have turned up some suggestive relationships between urinary catechol amines, perinatal birth complications and autonomic arousal.

Problem Solving in Schizophrenics.

Although it has been frequently alleged that the paranoid schizophrenic's mental functioning is better preserved than that of other schizophrenic patients, a number of recent studies cast some doubt regarding the validity of this notion. In a previous study here, a small group of paranoid schizophrenics showed marked inefficiency in problem solving performance as compared to a group of chronic undifferentiated schizophrenics. To check this finding, we conducted a study on larger groups of subjects and found

that the chronic undifferentiated schizophrenics always obtained higher scores on the problem solving task than did the paranoid schizophrenics. It was also found that the paranoid's performance was disrupted by increasing problem size or objective uncertainty and also when problems involved a reversal of the information cue which necessitated a change in set. The chronic undifferentiated patients showed losses in score only when problem size was increased. The low scores of the paranoid schizophrenics appeared to be due to a deficiency in a basic heuristic--the ability to deal with sets of objects.

Other Psychopathology.

Deficits in attention and, in some cases, their autonomic concomitants, and their changes with pharmacological or surgical therapy are being studied in three groups of patients in which such deficits are thought to be a primary symptom: patients with psychomotor epilepsy, narcoleptics, and minimally brain damaged (hyperactive) children.

In AER and perceptual style studies a variety of experimental approaches were used to further elucidate the concept of stimulus intensity control and its possible neurophysiological reflection in the observed augmenting-reducing experimental paradigm. Clinical applications in affective disorders have been further explored. Previous findings that manic-depressive (bipolar) patients show an "augmenting" AER style and that lithium carbonate is associated with a change toward "reducing" suggested the use of the AER measure to predict therapeutic response to lithium. Higher baseline AER augmenting values were found too in patients who showed a positive response to lithium, whether antimania or antidepression, than in patients with a negative or absent response. The ability to predict drug response from a physiologic measure is not only of clinical value but is of great interest from the point of view of biological factors in affective disorders. Since patients with a history only of depression (unipolar) show "reducing" AER and also show little antidepressant effect of lithium, this finding further supports the hypothesized biological differences between the two groups of patients.

Increased research activity has been focused on children who have what is now called the minimal brain dysfunction syndrome. The minimal brain dysfunction studies have included: A review of the literature and the writing of a published volume on the subject; a clinical investigation of the effect of lithium on minimally brain dysfunctioned children refractory to stimulants and phenothiazines; neuro-psychological correlates of minimal brain dysfunction; behavioral and biochemical studies of animal strains which may provide a model for exploring brain metabolism in the syndrome. These studies are still in progress, but should be ready for reporting next year.

Psychotherapy.

It is increasingly clear that progress in psychotherapy is dependent on our ability to identify and represent in objective fashion each of the elements of the following question: "What therapists, using what kinds of techniques, under what kinds of conditions, with what sorts of people, produce what kinds of effects?" Investigators in the Section on Personality aim to develop concepts and tools which warrant the sponsorship of a large-scale systematic research program. Such a program should permit the accumulation of data on standardized measures of the essential variables, i.e. patient, therapist, techniques, setting, and outcome. With this general goal in mind they have thus far worked in three areas: (1) Patient characteristics: Drs. Burgdorf and Parloff found that 56% of 756 exceptionally talented science students in college reported that they had "never considered" entering psychotherapy. The 44% who had considered psychotherapy included 20.5% who had never sought help and 23.5% who had sought treatment. Of those who entered

treatment only 12.5% (95 subjects) remained in treatment longer than five sessions. The group that "had considered but never entered psychotherapy" reported a lack of confidence in psychotherapy and the judgment that their problems were "not severe enough to warrant treatment." Reasons such as "lack of awareness of psychiatric facilities," "lack of money," and "fear of stigma" were only rarely given. Personality measures obtained while the students were yet in high school were strongly associated with subsequent help seeking behavior. The predictive efficiency of 10 personality measures was found to be stable on a replication sample. Personality data also differentiated those subjects who had never considered psychotherapy from all the others, and could predict, but with less efficiency, how long a subject who enters therapy will remain in treatment. The data obtained thus far do not, however, permit discrimination between those who consider seeking help but do not enter therapy and those who consider and actually do enter therapy. It appears, therefore, that the most critical step in the help seeking process -- that of making a decision to enter treatment -- is, paradoxically, the least predictable. Perhaps the decision to seek or not to seek help may be critically influenced by events in the immediate environment (e.g. attitudes of peers, group mores, experience of friends who entered psychotherapy, etc.). (2) Theory development: Dr. Stanley Greenspan, on the basis of his training, experience and an intensive review of the literature, has proposed an integration of psychodynamic and instrumental learning concepts. One of the major functions of his revised conception is to aid psycho-dynamically-oriented therapists in attending more to those environmental variables which may inadvertently be reinforcing and thereby maintaining maladaptive behaviors of the patient. He is also testing his model at a residential treatment clinic and in a classroom situation since this extension of the concept of intrapsychic determinants of behavior may be useful in its application to educational problems and to the treatment of children and adolescents in an institutional setting. (3) Mechanisms of change and instrument development: In collaboration with Dr. Martin Katz, Chief, Clinical Research Branch, NIMH, Dr. Parloff has participated in a series of conferences with other researchers to develop a standard set of outcome measures in the assessment of patient change and psychotherapy outcome.

Drs. Parloff, Dittmann, and Boomer have devised an instrument permitting a reliable review of psychotherapy reports and assessment of the adequacy of the study and the adequacy of the interpretations of the findings. This instrument has been applied to the group psychotherapy literature. The revised "findings" are in many instances at variance with those previously reported in research summaries and evaluations.

The effort to identify mechanisms and techniques for enhancing psychotherapy has involved a continuing study of a variety of encounter groups. Pilot work in utilizing some procedures borrowed from encounter groups, T-groups, and Gestalt therapy has been undertaken to enhance two important conditions of treatment: 1) Group cohesiveness; 2) The frequency and intensity of the affective experiences of the participants. In cooperation with Dr. Martin Katz and his staff, research plans for assessing the effects of specific encounter techniques with specified participants are being developed.

Behavior Genetics.

In addition to the genetic studies of schizophrenia and other disorders mentioned above, interest in the Laboratory is spreading to the role of genetics with respect to other behavioral indices.

Using a method of intraclass correlations, we have found considerable intra-twin pair similarity on various measures of arousal levels, but somewhat less similarity on stress and responsivity, and even less on behavioral measures. One autonomic variable, skin conductance, is being reanalyzed on the basis of "range corrected" values in order to remove a large source of variation which may be unrelated to psychopathology. Heart rate variability is being studied by means of spectral analysis and the autoregressive model. In order to assess the relative importance of genetic and environmental factors, monozygotic and dizygotic normal twins are being studied using measures of autonomic and psychomotor functioning, averaged evoked response (AER) procedures, a battery of perceptual tasks, questionnaires and interviews.

Perceptual Development.

Collaborative research in association with the Eye Research Foundation has continued this year on (1) the assessment of the discriminative capacity of infants and (2) investigation of the mechanisms governing the acquisition of new discriminations in infancy.

With regard to the assessment of discriminative capacity a study was initiated concerning the properties (eyes, nose, mouth, or their configured arrangements) which predominate in the four-month-old's perception of the human face. Previous research suggested that at four months the eyes are seen as a horizontal pairing in the upper part of the face rather than as unstructured elements, and that they predominate over the nose and mouth features. To evaluate this possibility, total fixation time to a regular face was compared for different groups of infants following prolonged exposure to various distorted versions of the face. Presumably, the greater the perceived difference between the regular face and the previously exposed distortion, the longer the looking time to the former. The distortions were of four general types--eyes, nose-mouth, all features, and face contour; they entailed both outright removal of features as well as dissolution of their configured arrangements. Although the experiment is not yet completed, the data thus far collected indicate that the eyes are more important than the nose and mouth in the face perception of four-month-olds and that the horizontal arrangement of the eyes in the upper part of the head is critical to face perception.

In another approach to assessing infant discriminative capacities, construction has just been completed on an infant discrimination training apparatus. The equipment permits presentation of two- or three-dimensional discriminative stimuli, which signal to the infant when one of his responses (a head-turn) will lead to reinforcement (combinations of peek-a-boo faces and mothers' voices). With this device we are currently preparing a series of experiments to determine whether young infants possess perceptual constancies. At issue here is whether constancies are achieved prior to movement

in space and how early in life visual information may become predominant over tactual/kinaesthetic information in human perceptual organization.

The discrimination training apparatus will also permit us to teach infants discriminations which they may have not yet mastered in their natural surround, and thus to investigate in a systematic way the conditions under which discriminations are achieved. Currently we are planning a broad inquiry into the roles of responding and differential reinforcement in the acquisition of early discriminations, i.e., whether the infant must actively respond to signaling stimuli in order to discriminate them or whether he can learn by passive observation alone; and whether different stimuli must be associated with differential consequences in order to learn to discriminate them or whether exposure to stimulus differences without correlated consequences is sufficient in itself for discriminative learning.

Biological factors important in perceptual augmenting and reducing are also being explored in studies of the effect of handedness, hemisphere of recording, and sex. New AER measures of perceptual behavior are being developed with studies of stimulus information content and contrast effects. A significant advance in AER and psychophysical technology was made with the development of "ERL", a high level computer language for programming experiments. ERL allows the investigator to specify the experimental design, present visual and auditory stimuli and record psychophysical data using a "natural" or English-like language rather than assembly type code.

Development of Behavior.

In a study carried out in Israel, male infants from four child-rearing environments (residential institution, kibbutz, youngest-child town family home, and only-child town family home) were observed under natural conditions at age two, six, and eight months. Four responses of the caretaker and/or mother representing the discrete behaviors of the environment were studied: Talking, Gross contact (comprised of picking-up, carrying, changing position, supporting), Fine contact (comprised of tickling, nuzzling, hugging, kissing, patting), and Smiling. The five child behaviors studied were Watching, Vocalizing, Smiling, Crying (including fussing), and Motor acts.

The first analyses have dealt with caretaker and child behavior counts for the entire observation day, ignoring their concurrent and sequential contingencies. For three of the caretaker behaviors, Gross contact, Fine contact, and Smiles, the child-rearing group means rank-ordered (from highest to lowest): Only-child, Kibbutz, Youngest-child, Institution. The only exception to this pattern was Talking, where the Youngest-child group mean was higher than the Kibbutz mean. These results for full-day counts indicate that the behaviors of the Kibbutz child's mother and caretaker together provide him with stimulus provisions rather like the pattern provided infants by mothers in nuclear-family homes and, indeed, in that frame often more like that provided to Only- than to Youngest-children. In that context, the mean number of Adult Talk and Smile responses tended to increase with child age, while Gross Contact and Fine Contact means remained constant.

The pattern of behaviors exhibited to the child was also found to depend on setting -- that is, whether the adult was providing care to her infant (feeding, bathing, diapering, or dressing him, termed "caretaking time") or whether she was simply present but not providing care, termed "pure-social time". Caretaking time comprised but a small fraction of the time adults were in the vicinity of their charges. In the Only- and Youngest-child nuclear family home settings, on the average more of each of the four classes of adult behaviors were provided to the children during Pure-social than during Caretaking time. This difference was less pronounced in the Kibbutz setting and reversed in the Institution setting. Thus, Institution infants received most of their stimulation from caretakers during the rather small portion of the day when they received bodily care.

With the exception of Watching (looking), a basically similar mean result pattern was found for each of the five discrete infant behavior classes observed in the presence of caretakers: the highest mean was found for the Only-child group, the lowest mean for the Institution group, with the Kibbutz and Youngest-child group means intermediate. However, for Watching responses the mean pattern changes according to the age of the children.

The mean patterns for child behavior in Pure-social and Caretaking settings were also similar to those for the adult behaviors in those settings. Only- and Youngest-child group means were higher during Pure-social than during Caretaking time, while the similar Kibbutz pattern was less marked between the two settings. Again, there were more child behaviors exhibited in the Institution during Caretaking than during Pure-social settings.

It is difficult to assign the label "cause" and "effect" differentially to the adult and child behaviors. It seems prudent in an in vitro analysis that sums behavior over the entire day separately for the infant and for his caretaker to report only the very similar patterns of adult and child behaviors examined in terms of age and environmental group membership as well as of Pure-social vs. Caretaking setting. In subsequent analyses, we shall be examining the contingent relations within interaction sequences that occurred between child and adult behaviors.

During the present year, we sought to relate our data on learning to more general principles of behavioral organization which might be characteristic of mammalian infants. Our research was concerned primarily with the following topics: (1) search for continuity of behavior over prolonged periods of time; (2) further experimental analysis of response components of the feeding sequence, including especially sucking behavior; (3) experimental synthesis of behavior in operant conditioning situations; and (4) stimulus control of instrumental crawling behavior.

Continuity of behavior in infancy. One assumption concerning behavior is that it is a "sometime" or episodic event, to be understood in terms of variables or vectors operative only during stimulus presentation or during trials in learning situations. An alternative view holds that behavior has larger organizational properties which transcend successive stimulus presentations and the mere succession of learning trials. Much of the data on neonatal behavior in dogs that we have analyzed during the past year are

consistent with the latter view. For example, neonatal dogs (that is, dogs less than two weeks of age) yielded orderly and typically linear curves of general bodily activity overnight plotted on half-hour periods. Every 2 minutes these puppies were subjected to a short-term, mildly aversive air stream which they could postpone for 2 minutes by simply moving enough to produce one count on the activity meter. The activity curves indicated that no special local behavioral process had supervened during the single overnight session to change the course of bodily activity.

Another example: An animal evincing an especially high rate of sucking was tested to determine how long he would suck for milk if we used as the nonresponse criterion 2 minutes of nonsucking. The puppy sucked for about 2 and 1/2 hours. This sucking bout is an especially striking example of continuous behavioral maintenance in the neonatal dog. During the latter part of the session milk flowed almost continuously out of the puppy's mouth, yet it continued sucking. The 2 and 1/2 hours matched the maximal sucking performance of acute physiological preparations tested by other investigators. They found that puppies whose stomachs had been anesthetized sometimes sucked for as long as 2 and 1/2 hours.

Experimental analysis of feeding sequence. The mammalian feeding sequence, as exemplified in canine neonates, consists of four general categories of behavior and a total of nine response classes. The feeding sequence ends with stomach filling, which is an event requiring that the puppy: (a) approach and touch the dam; (b) approach, latch on, manipulate, and suck a nipple; (c) obtain milk in its mouth and then swallow it; and (d) fill its stomach with milk. With the exception of swallowing, we have studied each of the foregoing response classes intensively in many experimental situations. During the past year we continued our studies of sucking per se, examining in particular the dynamics of exteroceptive stimulus control of sucking. We found that resilient water-filled nipples yielded higher rates of sucking than hard or lumpy tubing-filled nipples. Within-subjects analysis yielded systematic and statistically highly significant differences which were due to the exclusion of extraneous variables, but between-subjects comparisons yielded only chance differences.

These findings imply that unless group comparison is essential on theoretical or practical grounds, the investigator of human infancy should try to utilize within-subjects designs in his studies. We also examined the effect of 10, 15, 20, and 25 mm. length nipples on nonnutritive sucking. The 15 mm. length was optimal in that the rate of sucking and amplitude of sucking tended to fall off when a length other than the 15 mm. nipple was used. Moderate vs. overnight food deprivation had no systematic effects on the sucking measures, showing that under some conditions external stimulus control of sucking is far more powerful than internal physiological state.

Experimental synthesis of behavior in operant conditioning situations. The method of analysis into constituent elements is so popular in science and in behavioral research that many equate it with science itself. This is one reason for the popularity of reductionistic thinking in behavioral sciences. However, it is absolutely essential if we are to understand the

larger units of organization of behavior to study systematically how these larger units are synthesized out of the more elementary constituents. To this end, we have begun a series of experiments in an operant key-lifting situation, utilizing neonatal and infant dogs as subjects. To solve the problem and to display organized, orderly, and adaptive (milk-obtaining) behavior in our operant key-lifting situation, the puppy must not only lift the key but, then, find the nipple, latch on it, suck on it, leave the site of nipple when it is retracted from the experimental space, and, then, resume the necessary key lifting again. At various points in this sequence, as it is repeated in a session lasting many minutes, the puppy may fail either because he perseverates in behavior which he should give up or because he fails to emit behavior appropriate for that point in the sequence. We have found that puppies will learn to lift the key with their noses throughout many sessions, even when as many as nine or 10 key lifts are required to bring the nipple into the compartment only once. We have also found that when milk is omitted, the key-lifting behavior extinguishes, with or without continuation of nipple insertion. This means that nonnutritive sucking alone does not act as a reinforcer in the situation. Milk, however, is absolutely essential, for when the same puppies have milk reintroduced in the situation, the effects of extinction are counteracted and key-lifting behavior is resumed at essentially the same rate it was occurring before milk was omitted.

The powerful effect of milk as a reinforcer suggested that the operant key-lifting situation would be an excellent one in which to study further the locus of milk reinforcement itself. Is mouth stimulation by milk alone necessary? Or, is stomach stimulation alone necessary? Or, does the reinforcing effect require both mouth and stomach stimulation by milk? We had previously found that milk entering the stomach while bypassing the mouth acted as a reasonably stable reinforcer when made contingent on sucking. Accordingly, we tried to train puppies to life the key when key lifting was followed by direct intragastric injection of milk. The experiments were complete failures. The puppies not only did not learn the key lifting but became extremely lethargic. Instead of gaining behavior, the puppies seemed to lose it. This and additional studies indicated that when sucking is studied, intragastric milk injection has an apparent reinforcing effect. However, when the puppy must "synthesize" divergent elements of the feeding sequence into a smoothly flowing adaptive behavioral pattern, intragastric milk injection fails utterly to do the job.

The generally suppressive effect on behavior of intragastric milk injection is reminiscent of our data obtained when demonstrating that feeding puppies by gavage suppresses their behavior in direct proportion to the amount of stomach load. The suppressive effect is also comparable to certain manifestations of behavior in tests where we have studied electrical brain stimulation. For example, when neonatal puppies were trained to crawl in a T-maze, using only electrical stimulation of the brain as a source of reinforcement, it was found that the puppies tended to make the correct response whenever they moved. But, there was some tendency for the puppies to stop moving and, thus, fail to make a choice. We have concluded, therefore, that both intragastric milk injection and electrical brain stimulation, as we have studied them in the neonatal puppy, are incomplete reinforcers. Something is lacking with respect to behavioral maintenance when they are used in

learning situations.

After the key-lifting response was learned, some subjects showed a markedly aberrant pattern of behavior. This was a blocking of the key-lifting sequence by an undue prolongation of general bodily inactivity correlated with sucklike movements of the mouth which we have labelled TOR (tongue-on-roof-of-mouth sucking) and TOF (tongue-on-floor-of-mouth) sucking. In either case, the posture of the puppy is dominated by extension and general immobilization. The abnormality occurs during postreinforcement pausing, i.e., after retraction of the milk-containing nipple from the experimental space, but is absent during extinction when milk is omitted. This shows that the abnormality is not due to some kind of physiological or neurological deficit in the ordinary sense.

This phenomenon may be related to displaced activities of animals under natural conditions, the behaviors reported or described as instinctive drift by the Brelands, and the so-called interim or collateral behavior described by operant conditioning researchers, including psychotic behaviors as they occur in mental patients studied in operant conditioning situations. It is possible the maladaptive behavior we have discovered in neonatal puppies may provide an experimental model for the beginnings of severe behavior disorder later on. We plan to test this possibility.

Stimulus control of instrumental crawling behavior in neonatal dogs. Differential reinforcement in the presence of distinctive cues can produce discriminated responsiveness in canine neonates. From the mere fact of successful discrimination, however, it is not possible to describe precisely the nature of the stimulus control. The product of such learning could be: (1) inhibition to the appropriate stimulus; (2) excitation to the appropriate stimulus; or (3) both excitation and inhibition to the appropriate stimulus. Alternatively, one may regard excitation and inhibition as largely physiological concepts and view discrimination learning as a combination of the behavioral processes of conditioning and extinction. The problem then becomes largely one of determining relative strengths and stabilities of the processes of conditioning and extinction during or after successful learning.

Using milk as a reinforcer and plastic vs. cloth or wood vs. cloth as cues in a double-alley apparatus, we found that changing the cues (generalization tests) in the positive alley disrupted the crawling behavior reliably, but that changing the cues in the negative alley had no reliable effect. We have also found that reversal training was correlated with fast conditioning to the positive (formerly negative) cue but correlated with slow extinction to the negative (formerly positive) cue.

The differences in the cue-change (generalization) tests and the inequality in stability of conditioning vs. extinction (the former being much more resistant to the changed conditions of reinforcement than the latter) are consistent with the assumption that inhibition was relatively weak in neonatal dogs. They also are consistent with the assumption that conditioning and extinction are not mirror images of each other in the situation studied. Indeed, there was some evidence that responding in the negative alley might best be described as characteristic of omission of a positive reinforcer rather than of presentation of inhibitory stimulation.

The dissolution of social organization through overcrowding in mice. Every species fabricates enough biological replicates of its own kind to insure adequate replacement following the normal toll taken by aging, disease, hunger, predation, inclement weather, shortage of physical resources, and migration. Dr. John B. Calhoun constructed physical environments that essentially removed all of these debilitating and disposing variables, except for aging. The population inhabiting the largest environment has been permitted to survive. However, the other populations were not terminated until data from them indicated that their final history would have continued along a similar course. Following an initial period of stress accompanying their introduction, the eight colonizers of the largest environment initiated a period of rapid population growth that continued until most of the physical space became filled with organized small social groups of adults, each of which numbered 10 to 12 individuals. Fourteen such groups, totalling 150 adults, filled the physical space socially.

In the normal ecological setting, such a number of adults would have found it necessary to cope with fewer than 45 maturing individuals. However, the elimination of most of the debilitating and disposing variables enabled 10 times this number to survive. Most of this ten-fold number of youthful mice had undergone sufficiently adequate physical and social nurturance to provide them with the behavioral capacity to seek entry into the social system. Except for a very few who were able to replace the older members of established groups, the attempts to gain social incorporation by most of this young adult horde were rebuffed. They gradually withdrew physically by reducing motor activity and by assembling in large aggregates in less used space.

As a consequence of their rejection they no longer initiated interactions with socially organized associates, nor exhibited behavior that would elicit actions from them. However, minor changes in ambient stimuli provoked violent episodes of aggression among these withdrawn, rejected individuals, leading to a chronic state of extreme physiological stress. With the inception of this phase of social rejection the rate of population growth became markedly depressed, primarily as a result of inability to rear young by the later born females.

However, females of established groups continued to reproduce until 1600 more weaned young were added. Although many of these young received adequate physiological nurturance, they were exposed to early and intense social rejection, as reflected by their being bitten by their mothers just prior to weaning--a very abnormal behavior by lactating females. Once weaned, two other conditions interfered with normal behavior development. Mechanical interruption of action cycles in a milieu of many associations prevented completion of intended behaviors. Furthermore, the stochastics of interaction in the presence of excessive numbers of associates makes it difficult for any one individual to encounter another in a motivational state compatible with satisfying the actor's own need. As a consequence most of these later born individuals never learned those complex behaviors of social relating, aggression, courtship, mating, and maternal behavior which are requisite for survival of the species; they remained physiologically unstressed.

Gradually the previously socially organized members of the population reached menopause with no associates having the capacity to replace them. As a result the population has now declined from a peak of 2200 individuals to 1400 through normal aging-related mortality. Most of the survivors have now nearly all attained menopause during the 14 months since the last viable young was born. We do not anticipate any further reproduction. Individuals removed and placed in similar, but low density, habitats exhibit nearly a total loss of capability for social organization and reproductive capacity. Although these studies were conducted with mice, the findings may have application to other species, including man.

Processes of Communication.

Dr. Boomer's research in the area of psycholinguistics has this year focused on identifying the complex processes which permit the listener to comprehend the speech production of others. Dr. Boomer has hypothesized that the listener attends to "chunks" of speech which are identified on the basis of intonational patterns. The intonation unit may comprise from one to seven words, and has been called a "phonemic clause." Such units are held in short-term memory and processed as patterns of sound, syntax, and sense.

Work by Kahneman and Beatty demonstrated that subjects' pupils dilated steadily as they attempted to keep in memory a string of digits, and contracted as these digits were recalled. If pupillary diameter is in fact an index of the load on short-term memory and if the phonemic clause is a functional unit of speech decoding, then each clause should accumulate in short-term memory until the speech juncture signals that the unit is completed. As a subject listens to speech, a gradient of pupillary expansion should occur over the 1000-1100 msec. duration of a phonemic clause; however, at the point of the juncture a quick contraction should occur for the juncture marks the end of the clause. Currently, the Kahneman-Beatty task is being used to screen subjects for a test of these hypotheses.

Dr. Dittmann's work this year challenges two basic assumptions underlying the discipline of kinesics: (1) that movements are discrete events analagous to speech events; (2) that movement events are organized into larger units in a hierarchical series by some internal organization parallel to the syntax and grammar of language.

While a few movements are classifiable into discrete categories (such as the head nod and changes in gaze direction between conversationalists), continuous movements and movements which accompany the rhythmical patterns of speech but do not fall into recurring categories do not qualify as elements that can be combined into a language-like system. He concludes that there does not appear to be a sufficient "vocabulary" for a body movement language parallel to spoken language.

Dr. Dittmann undertook further studies of respiration during speech in order (1) to describe how breathing fits in with the rhythmic patterns of speech, and (2) to learn how both respiration and speech systems accommodate to stress. He finds that the formation of rhythmical units in speech and the

requirements for breathing are interlaced so that inspirations come for the most part at unit boundaries, or junctures in speech. Individual differences, however, are very large. Additional data indicate that rhythmical speech patterns are interrupted by inspirations more under mild stress than under baseline conditions, but not as much as breathing is increased. There is a 25% increase in proportion of inspirations at hesitation pauses, but a 39% increase in respiration rate with mild exercise.

Attribute attainment studies.

A series of attribute identification experiments was completed during the past year. These studies were controlled in real-time by computer programs that interact with the subject's selection. As a result, the amount of information obtained about each solution effort was maximized by preventing the operation of random factors that lead to solution by guessing, thus eliminating an important source of variability not controlled by other investigators in the field. The problems presented were governed by four logical connectives: "or"; "if...then---"; "...if and only if---"; and "either...or ---." In the psychological literature on concept identification, there has been considerable disagreement regarding the difficulty of these various concept rules. Results of the computer controlled studies support the hypothesis that the subjective difficulty of the various concepts, as estimated from performance measures, is in agreement with objective measures of the complexity of the problem spaces generated by the logical connectives. Specifically, the "either...or---" and "...if and only if---" concept rules have an objective problem space of 12 alternatives and are found to be subjectively easier than the "or" and "if...then---" rules which have a problem space of 24 alternatives. This is an outcome often sought but seldom realized by other investigators. The data also suggest that many of the failures to obtain agreement between performance and objective measures of difficulty result from one or both of the following: a) an inadequate index of performance (i.e., investigators using total number of trials or errors to solution); and b) failure to separate the process of eliciting information from the problem of interpreting or evaluating it.

Another study was concerned with estimating the effects of memory strain on attribute identification. Half of the subjects were required to record their selections and information feedback on forms provided for this purpose. The other subjects were not allowed to record this information. Analysis of the number of trials to solve each problem revealed no statistically significant differences between the group with the memory aid and the group that had to remember the same information.

Time judgment and circadian rhythm. The basis for the ability to perceive the passage of time is obscure but it is generally thought to arise from cyclic processes such as variation in metabolic rate or the EEG activity of the brain. These processes differ markedly between the normal resting state of sleep and the normal waking state. Moreover, there are progressive changes during sleep. It is convenient, though not necessarily physiologically correct, to speak of an "internal clock" whose rate is reflected in behavioral judgments of the passage of time. We sought to determine whether the rate of

the "internal clock" differs in the sleep and daytime conditions and whether it varies during the night.

Human subjects were awakened periodically during the night and tested in two ways. In one experiment short time intervals were presented, and the subjects estimated the durations of those intervals. In another experiment subjects were asked at each awakening to estimate the time that had elapsed since the preceding awakening. EEG activity was recorded continuously during the entire night. Other subjects have been tested repetitively during the day on successive days, and an experiment is planned in which testing will occur repeatedly over a single day.

Results did not differ significantly for daytime and nighttime testing nor for different kinds of EEG activity occurring during or preceding the time interval being estimated. There was some apparent change in internal clock rate during the course of the night, but this change was similar to that obtained in the day-to-day testing.

The findings suggest that the internal clock rate is not a function of circadian rhythms and is, in fact, much more stable than is currently supposed. If so, an important implication is that, contrary to wide belief, the perception of time may not differ in other conditions such as anxiety, euphoria, drug states, and psychopathology, and that the capacity to perceive events may depend fundamentally upon the capacity to perceive time, rather than that the time sense is a byproduct of perceived external and internal events.

Studies of creativity. In research on creativity, no consensus exists with regard to its conception, theory, or operational measurement. Many studies report relationships between "creativity" and such variables as intelligence, personality, social background, attitudes, values, beliefs, etc. Since there is no unanimity regarding the criteria of creativity, the generalizability of the reported correlates of creativity may well be limited.

Drs. Parloff and Burgdorf undertook to test whether different patterns of correlates would be found when three different criteria of creativity were applied to the same set of subjects. The criteria were (1) scores on "creativity tests" (Test); (2) judgments of the creativity of a piece of research produced independently by each subject (Product); and (3) levels of achievements and awards -- local, State, or National (Recognition).

Data were obtained from 351 subjects (87% of the surveyed sample). Such data included measures of personality, interests, activities, aptitudes, achievements, intellectual performance, social history, etc.

Six widely used "paper and pencil" tests of creativity were employed to identify the "Test Creativity" groups. None of the tests alleged to measure creativity was found to relate in the expected manner to any other measure of creative ability. None of the "Test" identified creativity scores was significantly related to any of a variety of measures of scientific activity, achievement, personality traits, or activity and achievement in

extracurricular areas other than science. These "creativity" tests were, however, found to be positively associated with measures of academic aptitude and academic achievement. This suggests that the scores on the tests of creativity are also measures of intelligence.

The Product and Recognition criteria groups revealed quite different patterns of correlates. When the Recognition criterion was used, it was found that creativity scores were independent of measures of academic aptitude, socioeconomic status and other family background indicators. However, strong associations were found with measures of activity and achievement in extra-academic fields other than science. The reverse was found when the Product criterion of creativity was used. Samples identified on the basis of Product and Recognition scores both showed positive correlations with measures of scientific activity and achievement, creativity self ratings, and personality traits widely believed to be related to creativity. However, the strength of association was consistently greater for the Recognition than for the Product sample.

The Recognition criterion sample behaved most in accord with theory-generated expectation, while the Test criterion sample was least in accord with expectation.

The findings suggest that it is more useful to develop measures of creative ability by utilizing a criterion-centered, empirical model (in the development of instruments to measure intelligence and personality) than to employ the currently fashionable hypothetico-deductive model.

ANNUAL REPORT OF THE LABORATORY OF SOCIO-ENVIRONMENTAL STUDIES

National Institute of Mental Health

July 1, 1970 through June 30, 1971

Melvin L. Kohn, Chief

Much of our research, now as throughout the history of this Laboratory, is concerned with societal influences upon the family and upon the social and psychological development of children. In the current emphasis on child mental health, though, it is important to remember that there is both continuity and change in the individual's development; the adult as well as the child is responsive to his social environment; and the family is only one of the major social institutions that affect man's personality and his behavior. Our program of research emphasizes the family and child development, but tries to recognize the importance of other social institutions and other ages. These efforts are reflected, for example, in our study of the effects of occupational experience upon men and in our plans for an inquiry into the social-structural sources of stress.

At a time of serious cutbacks in personnel, the continuing momentum of our research has been based on the use of ad hoc arrangements and on the fortunate fact that some of our investigators had collected large bodies of data prior to the cutbacks. These ad hoc arrangements have not been sufficient to sustain our once-flourishing program of cross-national comparative research; that program is but a shadow of its former self. Nor will ad hoc arrangements be sufficient to assure the continued vitality and originality of our research: they can keep existing research going, but do not provide for new endeavors. The future of this Laboratory will be foretold less by the findings we report here than by our ability to carry out new endeavors that are only now being planned.

In the following summaries, the emphasis is necessarily on new findings and new plans. It should be noted in passing, though, that these summaries do not fully illustrate the scope and diversity of the Laboratory's program, for they ignore those projects whose principal activities this year were data-collection or the preparation of data for analysis--in particular, research in schizophrenia and in behavior genetics. On these topics we have had much to report in the past and hopefully will have more to report in the future.

PARENTAL CARE AND CHILD BEHAVIOR IN JAPAN AND THE UNITED STATES

William Caudill's systematic observations of comparable samples of mother-infant pairs in Japan and the United States led him to conclude that even by three-to-four-months of age Japanese and American infants show characteristic, culturally-appropriate differences in behavior. He also concluded that these differences are meaningfully linked to observed differences in Japanese and American mothers' child-rearing practices.

His interpretation was that the imprint of culture--transmitted from mother to child--could be seen even at this early age. But there remained another possibility: that Japanese infants behave differently from Americans, not because their mothers treat them differently, but because they are genetically distinct.

This year, Caudill (in collaboration with Lois Frost, a graduate student in anthropology at Sacramento State College) has had an opportunity to test the latter interpretation by studying Japanese-American families. Mrs. Frost used Caudill's observational techniques to study a sample of third-generation Japanese-American mothers of three-to-four months old infants. This group is of particular theoretical interest because the infants are genetically Japanese but are being reared by parents who, on the basis of past research findings, could be expected to have values and to employ child-rearing practices similar to those of white middle-class Americans.

Caudill's procedure in analyzing these data was to make three sets of paired comparisons (Japanese Americans with Japanese, Japanese Americans with other Americans, and Japanese with Caucasian Americans). These comparisons, as hypothesized, show Japanese-American mothers to be much more like other American than like Japanese mothers in their style of interaction with their infants: they are apt to engage in active stimulation of the infants, especially by the use of a great deal of lively chatting, whereas Japanese mothers are more likely to lull and soothe the infants. Correspondingly, Japanese-American babies behave more like other American than like Japanese babies: they are more physically active, they vocalize more, and they vocalize happily more of the time than do Japanese infants.

In some respects, though, Japanese-American mothers have retained elements of a Japanese style of mothering. They play with their babies more than other American mothers do, and they engage more in verbal lulling and carrying of their babies. The babies, correspondingly, play by themselves less, and suck their fingers and other nonnutritive objectives less than other American babies do. On the whole, then, Japanese-American mothers have come to behave like other American mothers, but have retained some distinctive elements of their Japanese cultural heritage. And Japanese-American babies behave much like white middle-class American babies, but with a few distinctively Japanese characteristics linked to those elements of Japanese child-rearing practice retained by their mothers.

The data thus argue against a genetic interpretation of the behavioral differences between Japanese and American infants. Instead, they suggest that both cultural change and cultural persistence operate to influence the behavior of Japanese-American mothers and their babies.

HEALTH ORIENTATIONS OF CHILDREN

John Campbell is treating an essential question in child development--the transmission of values and attitudes in the family--by focusing on the development, by children, of orientations to health and illness. Health

orientations are of obvious practical importance; they also afford a strategic way of getting at a delimited range of values and attitudes that can be effectively studied.

The research is based on interviews and other data secured from 264 hospitalized children and their mothers. The development of indices of health orientation valid for both children and mothers posed a major methodological problem. Fortunately for the research, factor-analytic procedures revealed that the underlying structure of mothers' and children's belief-systems are basically the same. From a methodological perspective, this finding means that mothers and children can be measured on the same scales. Substantively, it supports the view that an important part of socialization involves processes whereby growing children increasingly adopt frames of reference similar to those of their elders.

The most likely process by which children develop adult orientations is for the parental perspective to provide the prototype for the views adopted by the child. If so, parent-child agreement in health orientations should be greater for older than for younger children. In general, the data of the present study do support this expectation. The greater similarity of mothers' and older children's views is evident in such diverse areas as their assessments of the child's functioning in the sick role, his risk-taking, and his responsibility for illness. These data suggest that the child learns many of his health orientations at his mother's knee.

There is, however, one important realm where older children are in no closer agreement with their mothers than are younger children: in their definitions of illness. For older and younger children alike, mother-child comparisons yield little more than chance agreement. On the average, though, the major themes emphasized by older children in their definitions of illness are more like those emphasized by adults than are those of younger children. Older children do come to develop adult definitions of health and illness, but apparently from processes of general social accretion rather than specifically from mother-to-child transmission of concepts. Campbell's further research will attempt to learn what these general processes may be.

THE EFFECTS OF CHILDREN'S BEHAVIOR ON ADULTS

Anecdotal evidence abounds about the influence of children on those who rear them, but there has been little systematic research directed to assessing the actual impact of children's behavior on their adult caretakers. Does the child influence the amount and kind of nurturance that his caretakers provide? Does the child's behavior affect the amount of stimulation, emotional support, or discouragement he receives from his caretakers? Marian Yarrow and Carolyn Waxler have recently addressed their experimental research to these questions.

An experimental design for studying the influence of the child on the adult is difficult to achieve. The most direct approach, varying children's behavior experimentally and observing resultant variations in

the adults' behavior, is obviously not feasible with young children. So an alternative approach was employed. Two women were trained to play highly nurturant and markedly less nurturant caretaker roles in handling small groups of preschool-age children. (Nurturant caretaking consisted of praising, helping, giving affection, and being respectful when exercising control. Nonnurturance was characterized by showing minimal attentiveness and employing critical evaluation or arbitrary control.) Each of the women performed both roles, with different groups of children. When playing either a nurturant or a nonnurturant role, the women were instructed to treat all children alike. Thus, an effort was made to standardize the adults' behavior. The impact of the children could then be assessed by measuring deviations from these standards.

In fact, the adult caretakers varied greatly in their treatment of individual children, even while adhering closely, overall, to the experimentally prescribed conditions of nurturance or nonnurturance. Under experimental conditions calling for nurturance, dependent, attention-seeking children successfully claimed more than their share of stimulation and support from the adult caretaker. Under nonnurturant experimental conditions, dependent children created more confrontations, thereby eliciting rejection by the caretaker. The caretakers behaved more negatively toward these children even at times when the children were making no demands on them.

The same behavior by boys and by girls elicited different reactions from the adults. They reacted more punitively toward boys than toward girls for disapproved acts, particularly when these acts manifested a lack of impulse-control.

Adult reactions to children's behavior were not always evident in their immediate responses, but sometimes became apparent later. For example, although the adults did not always respond immediately when children made nuisances of themselves, these children were often later singled out for negative attention, at times when they were not misbehaving.

Many studies of behavior modification have used adult reinforcement of the child's behavior as the vehicle for molding the child's behavior. The present study provided an opportunity to reverse the cast of characters, to see the child's response as reinforcing the behavior of the adult. When the child responds positively, by showing interest or affection, the adult is likely to initiate another positive contact quickly; on the other hand, nonreinforcement by the child results in much slower return by the adult. Adults' sensitivity to the actions of children thus closely parallels the often-demonstrated sensitivity of children to positive reinforcement by adults.

It is apparent from these findings that theories of socialization should be expanded to encompass the reciprocal effects of children on adults.

FATHER-ABSENCE AND SEX-ROLE IDENTIFICATION

Some years ago, Roger Burton and his mentor, John Whiting, proposed an interpretation of sex-role identification called the status-envy hypothesis--essentially, that a child comes to identify with the parent who controls resources the child deems important. Such an interpretation implies that a boy raised in a fatherless household would have difficulty in achieving sex-role identification as a male. Evidence from primitive societies suggested that this is indeed the case. There was also supporting evidence from modern societies, but this evidence was deemed suspect because father-absence was usually associated with illegitimacy or some other stigmatized situation.

To explore the problem further, Burton secured the help of Mother Mary Alban Holmes, headmistress of a Catholic school in Barbados, who provided the data with which to study the relationship between father-absence and sex-role identification in a society where father-absence bears relatively little stigma. These data consist of basic background information about the children attending the school, together with projective test materials from which it is possible to infer sex-role identification. Burton finds fairly substantial relationships between father-absence and indications of conflict in male sex-role identification. Moreover, the longer the boy had been in a fatherless household, the greater the conflict. The presence of other adult males, who might serve as models but who do not control important resources, does little to help.

There are also indications in the data that father-absence in the first two years of the boy's life may have especially serious effects.

NATURAL SELECTION AND THE ORIGIN OF LIFE

Gordon Allen is a behavior geneticist, whose usual province of interest includes such problems as the genetic contribution to mental disorder and the possible importance of social and psychological characteristics in evolutionary processes. He has, however, long been interested in the problem of the origin of life, and this year published a hypothesis to account for this phenomenon.

The difficulty with most formulations of the problem is that they must posit the chance origin of a self-reproducing entity, one with a highly complex self-copying mechanism--an exceedingly improbable event. Allen hypothesized, instead, that the origin of life is to be found in the reproduction of catalytic compounds by the environment:

> The first regular self-replication of ordered linear polymers on the earth was preceded by a period of evolution by natural selection among simpler organic molecules that did not serve as templates but reproduced by promoting other reactions critical for their own synthesis. These nonliving units of what may collectively have been life can be called "bions."

Bions would not individually have the capacity to mutate or the capacity to accumulate biological information, indispensable for evolution by natural selection. It can be shown, however, that a hypothetical system of bions together with their chemical environment would have both essential capacities.

The bion hypothesis, if strengthened, would tend to discourage the research effort being made in several laboratories to produce gene analogs under primitive earth conditions. Even if the hypothesis is not true for the historical origin of life on the earth, the theoretical possibility of natural selection without self-copying may require a reconceptualization of the role of the gene in biology.

CHILDREN'S PERCEPTIONS OF SOCIAL STRATIFICATION

As part of their research on children's self-conceptions, Morris Rosenberg and his collaborator, Roberta Simmons (of the University of Minnesota), investigated children's perceptions of the stratification system and their own place within that system. The data are based on a survey of a large, representative sample of students in the Baltimore Public Schools.

The focus of this part of the inquiry is the consequences for the social system of children's beliefs and attitudes. According to the classic functionalist theory of stratification, differentials in occupational prestige and income motivate people to invest time, energy, and resources in learning to do complex jobs whose performance is indispensable to society. It is apparent, however, that the existence of a system of unequal rewards and privileges is not in itself sufficient to induce children to acquire the training necessary for the performance of adult occupational roles. Certain perceptions and attitudes are also necessary to generate this motivation.

The first requirement is that children be aware of the system of occupational prestige in the society. The data indicate that this condition is eminently satisfied. As early as elementary school, children evaluate the prestige of various occupations in a rank-order almost identical to that of adults. Even for third graders, the correlation of children's and adults' ratings of occupational prestige is an astonishingly high 0.94.

A second functional requirement is that the individual thinks he has some reasonable chance of realizing his aspirations. The data show that although most children are well aware of socioeconomic, racial, and ethnic inequalities in opportunity, even those from disadvantaged backgrounds feel that their own personal prospects are good. Moreover, they confidently expect to surpass their fathers in income and occupational status. (Older children are even more likely than younger ones to expect to surpass their fathers--not so much because their aspirations have risen as because their judgments of their fathers' positions have fallen.)

Despite their awareness of differentials in occupational prestige, most children, even at high school levels, seem to have only a dim awareness of the nature of the social class system. This is particularly true of disadvantaged children. Rosenberg and Simmons point out that this limited understanding of the class system may mitigate hostility toward the social system by those who fail to realize their aspirations. In that sense, it is functional for the maintenance of social stability.

THE SOCIAL PSYCHOLOGICAL CORRELATES OF OCCUPATION

Three and four decades ago, students of occupation wrote fascinating case studies of how particular occupations--railroading and teaching are two prime examples--mold the lives of those who work at them. As research in this field has moved from descriptive accounts to more precise quantitative investigations, the focus has narrowed. Occupation has come to denote little more than occupational status--an important, but surely not the only important, facet. And the social psychology of occupations has come to mean the study of men's subjective reactions to their jobs--job satisfaction and occupational commitment.

Carmi Schooler and Melvin Kohn are engaged in a systematic effort to address the old problem, the effects of occupation on the man, with new methods. As in the earlier descriptive studies, the problem is the far-ranging social-psychological impact of the job on men's values, self-conception, social orientation, and intellectual functioning. This inquiry differs from the descriptive studies of particular occupations, though, in that it deals with a very broad range of occupations, using a representative sample of all employed men. The intent is to secure data about many aspects of men's occupational experience that might be pertinent to their social-psychological functioning.

This year's principal accomplishment has been the assessment of the comparative potency of these many dimensions of occupation, as judged by the strength of their relationships to values, orientation, and intellectual performance, and the classification of the more potent occupational dimensions into theoretically meaningful clusters. Together, these clusters define the structural imperatives of the job:

1. The organizational locus of the job (ownership, bureaucratization, and position in the supervisory hierarchy);

2. The conditions that facilitate or inhibit the exercise of occupational self-direction (closeness of supervision, routinization, and the substantive complexity of the work);

3. Job pressures (time pressure, overtime, heaviness of the work, and dirtiness); and

4. Uncertainties (the likelihood of a dramatic change in the man's situation, the probability of being held responsible for things outside of one's control, and the risk of loss of job or business).

These--independently of educational attainments, of one another, and of all the other dimensions of occupation that were measured--bear significantly on men's social-psychological functioning. By contrast, some facets of work that have been at the forefront of attention in occupational sociology prove to have little independent impact on values, orientation, and intellectual functioning. Thus, for example, extrinsic benefits conferred by the job, such as income and prestige, prove less potent than had been expected. And the interpersonal relations in which the job is embedded appear to affect social-psychological functioning only insofar as they are determinative of occupational self-direction.

These analyses also show that the principal relationships between the structural imperatives of the job and values, orientation, and intellectual functioning have face validity. Pressures and uncertainties, for example, bear more specifically on anxiety, while the substantive complexity of the work is pertinent to almost all aspects of social-psychological functioning.

At this point, there remain many important problems in establishing the directionality of the relationships. There is, fortunately, evidence that men's reports about their jobs are not appreciably biased by their own needs--for example, reports about time pressure are not much affected by how anxious the respondents are. The data also show that the findings are not attributable to age, race, religion, or other social characteristics. But the investigators have only begun to deal systematically with the questions of how much opportunity men have to mold their jobs, and how much real choice they have, with respect to each of the pivotal dimensions of occupation, in choosing and/or leaving jobs. Analyses are underway on all these issues.

THE "FIT" BETWEEN INDIVIDUAL AND COMMUNITY CHARACTERISTICS

Lindsley Williams (who is working with us by courtesy of HSMHA's Career Development Program) is combining the social-psychological data of the Occupations study with Census data about the principal communities in which the research was conducted, to see how the fit between individual and community characteristics affects social-psychological functioning.

One objective of this analysis is to see whether variations in values and orientations, from one urban setting to another, can be understood in terms of the differing social compositions of these communities. This analysis (as in Schooler and Kohn's analysis of occupations) is intended to go beyond a "nominal" level that treats each community (or occupation) as unique. Here, the approach is to focus on the underlying

dimensions of community structure, such as total population, density, occupational structure, educational distribution, and racial composition. Since the study is concerned with the overall organization of communities, attention will be given to the profile of each community as well as to its mean or median level. Any community can be characterized, for example, along a continuum from highly homogeneous to highly heterogeneous in its occupational distribution. It can also be characterized with respect to pronounced voids and excesses: compared to the rest of the country, Washington, D. C. has a disproportionate number of bureaucrats.

A second objective is to explore variations in values and orientation in terms of the individual's consonance with or dissonance from his social context; this entails juxtaposing information about the individual's own social characteristics with corresponding information, derived from the Census, for the community in which he lives. The question is one of fit--does it matter for one's values and orientation to be socially distinctive in one's community? There is evidence from earlier studies that it does, but the evidence is limited in scope and there has been no systematic effort to interpret which types of consonance and dissonance have what social psychological impact. This study is intended to be a systematic beginning of such an interpretation.

THE SOCIAL-STRUCTURAL ORIGINS OF STRESS

Leonard Pearlin, Frederic Ilfeld (of the NIMH Career Development Program), and Albert McQueen (a visiting scientist from Oberlin College) have been conducting a series of 40 intensive, unstructured interviews, primarily with black residents of inner-city areas, in preparation for an intended larger-scale study of the social origins of stress. By stress, the investigators mean any emotional burden experienced by individuals from which they attempt to remove themselves. In contrast to the previous studies that have emphasized unusual and extreme threats to safety, this research is directed to stress-producing events and experiences that can be traced to basic features of social organization.

A conceptualization of stress is the most critical task to which the intensive interviews have been directed. To establish empirical relationships between stress and particular social conditions, it is necessary to think of stress itself as specific and as responsive to identifiable conditions and events, rather than as a steady, enduring mental state. Such relatively enduring mental states as depression, anxiety, and apathy are more profitably viewed as consequences of continued exposure to stress, or as consequences of inadequate coping.

Three social conditions potentially productive of stress stand out in the exploratory interviews. The first arises when social prescriptions or proscriptions do not allow the expression of elements of self that the individual considers important. The dilemma has been voiced in the interviews in a variety of ways: by the woman who reports that she acts stupidly when in the company of men, so that they will accept her; by the

man or woman who feels that his friends don't know him as he really is; by the wife who must act submissively, although she has a higher regard for her own decision-making abilities than for her husband's; by a young man who sees himself as a champion of the underdog but whose job it is to collect delinquent bills.

A second stress-arousing condition arises from threats to one's social expectations posed by the behavior of others. Through the criss-crossing expectations that exist in the family, for example, one hears husbands express discontent with their wives as lovers, wives with their husbands as breadwinners, and parents with their children as students.

The third major social condition productive of personal stress arises from social obstacles to highly prized goals. This experience is especially poignant for lower-class people who are struggling to achieve upward social mobility.

Denial of self-expression, violation of expectations, and frustration of goal attainment are not experiences that afflict an unfortunate few who happen to be caught in a set of unusual circumstances. These are, instead, enduring and repeated features of daily life, probably touching everyone, although not with the same intensity. Because of the ubiquitousness of stress, the search for its origins will traverse several institutions: the family, occupation, interpersonal relations, and what has come to be called the societal opportunity structure.

Another issue pertains to mediating factors. It is evident that subjectively experienced stress is not a direct function of the social conditions to which an individual is exposed, but depends on his appraisal of these conditions. Several cognitive dimensions enter into this appraisal: principally, the importance he attributes to the given conditions; the extent to which he feels he can favorably modify impinging conditions; and whether he regards his future prospects optimistically or pessimistically.

Finally, the interviews have helped clarify some issues pertaining to coping. Some coping behaviors serve to modify the situation, either by defusing the stress-provoking elements or by enabling the person to step outside the orbit of their influence. Others serve to alter the appraisal process; for example, some respondents indicated that they reordered priorities or invoked new standards, thus alleviating stress by changing the perception and meaning of the stress-arousing situations. And some coping is directed primarily toward the management of the tension-state itself; these behaviors serve to modify neither the situation nor its meaning, but to relieve the individual from acute awareness of his feelings of stress.

Annual Report of the Laboratory of Cerebral Metabolism
National Institute of Mental Health
Louis Sokoloff, Chief
July 1, 1970 through June 30, 1971

The Laboratory of Cerebral Metabolism has finally established itself in its new quarters in Building 36, and its research program has regained the momentum interrupted by the move into the new building and the absence of its Laboratory Chief for fiscal year 1969 on a work assignment abroad. All research projects in progress prior to that time have now been reinstituted and extended into new and promising areas. Significant progress has been made in all of them.

Section on Developmental Neurochemistry
Louis Sokoloff, Chief

This Section has continued its heavy emphasis on the elucidation of the mechanism of action of thyroid hormones and their essential role in the development and maturation of the nervous system. Thyroid deficiency in early postnatal life leads to physical and intellectual dwarfism and has long been recognized as a not infrequent cause of mental deficiency. This project led several years ago to the discovery that thyroid hormones stimulate protein synthesis, an effect which is now recognized as the basis for many of the physiological actions of the hormones. The Section has been engaged in studies of the molecular mechanisms underlying this effect on protein synthesis in brain and other tissues. It has been found that the stimulation of protein synthesis is not a direct effect of the hormone but is mediated by the product of a prior reaction between the hormone and the mitochondrial fraction of the cell. The nature and identity of this product is being investigated with slow but steady progress. It appears to be a small, heat stable, acid-labile molecule which is not cyclic AMP nor any other known cyclic nucleotide. The possibility that it is a small polypeptide has not yet been excluded.

Two recent reports in the literature have questioned the role of mitochondria in the mechanism of the thyroid hormone effect. These have claimed that thyroxine could stimulate protein synthesis without any prior reaction with mitochondria. These alleged effects have been extensively investigated in this laboratory and have been proved beyond any doubt to be the result of technical artifacts in the procedures used by these other investigators. These results add, therefore, additional support to the thesis that the mitochondria contain the locus of the primary action of thyroid hormones on protein biosynthesis.

The interaction of thyroxine with mitochondria is known to be associated with an increase in mitochondrial ATPase activity. In contrast, it has been found that thyroxine inhibits microsomal ATPase activity, and this latter effect is unrelated to the actions on protein synthesis. This effect, which was also first discovered in this laboratory, is being studied to clarify its mechanism and physiological significance. There are a variety of microsomal ATPases, and thyroxine appears to inhibit both the Ca^{++}- and Mg^{++} -activated activities. Preliminary studies suggest that thyroxine may also affect the K^{+}- and Na^{+} -stimulated ATPase. The ion-activated ATPases are believed to be related to ion transport in and out of the cell and may be closely related to membrane functions which may be associated with excitability as well as many other cellular functions. It is hoped that further clarification of this effect of thyroid hormones may provide explanations of other effects of thyroid hormones not already explained by the effects on protein synthesis.

Studies on the effects of thyroxine, iodohistidine, histidine, and other amino acids on mitochondrial energy metabolism have been continued. The results of these studies indicate that iodohistidine, histidine, and a number of other amino acids, can increase the rates of respiration and coupled phosphorylation in freshly prepared intact rat liver mitochondria. These amino acids differ, therefore, from thyroxine which inhibits phosphorylation as well as the coupling of respiration and phosphorylation. The increase in the rate of phosphorylation observed with iodohistidine and other amino acids is not mediated through an effect on adenine nucleotide transport. Neither thyroxine nor iodohistidine has any effects on the affinity of AMP or ADP for the translocase or on the maximal rates of transport of AMP or ADP into mitochondria. The results of experiments just completed indicate that the increased rates of respiration and phosphorylation may be coupled to increases in cation transport and to the ejection of protons from the mitochondrion. Dramatically higher levels of calcium and potassium are found in mitochondria incubated with L-histidine as compared to those incubated without an added amino acid. These findings are of significance since it is known that stimulation of ion transport also stimulates respiration, and an effect of amino acids on these processes may be important for the regulation of intracellular energy metabolism

The Section has also continued its studies on the effects of thyroid hormones on the postnatal maturation of the nervous system. It was previously found that D(-)-β-hydroxybutyric dehydrogenase, a key enzyme in the utilization of ketone bodies, is low in the brain at birth, rises to a peak during maturation, and then, in contrast to other mitochondrial enzymes which remain constant, declines again in the mature brain. Since

starvation produces an increase in availability of the substrate for this enzyme through fat degradation, this enzyme is probably of major importance in protecting the brain from insufficiency of oxidizable substrate during nutritional deficiency. It has now been found that thyroxine strongly influences the developmental pattern of the enzyme in brain. Hyperthyroidism accelerates the rise of the enzyme level during postnatal maturation. Presumably hypothyroidism has the opposite effect although this is not yet proved because of difficulties in producing hypothyroidism in animals this early in life. This finding offers further definition of the role of thyroid hormones in promoting maturation of the CNS.

During the past year the Section reactivated a previous project on alcoholism which was inactive the previous year because of limitations in personnel and the dislocations associated with the move into Building 36. This project is carried out in collaboration with Dr. Neil H. Raskin, who was formerly a Research Associate in this Section but is presently at the Department of Neurology, University of California Medical Center, San Francisco. This project was previously responsible for the first demonstration of the presence of alcohol dehydrogenase the enzyme responsible for the metabolism of ethanol, in the brain. It was found during the last year that this enzyme activity is increased 50% in brain, but not at all in liver, by prolonged alcohol ingestion. This effect has important implications to the biochemical mechanisms underlying the development of tolerance to alcohol and to alcohol-withdrawal syndromes, such as delirium tremens.

Studies of the regional cerebral circulation have also been continued. The studies of the changes in blood flow of the individual component structures of the brain from birth to maturity in the dog are almost completed. The results indicate an increase in gray matter blood flow from birth to maturity commensurate with the maturation of neuronal activity. Blood flow in white matter is highest during the period of maximum rates of myelinization and reflects probably the higher energy demands during this period for myelin biosynthesis. Dr. Kennedy has completed his investigations of the effects of high oxygen concentrations on the cerebral circulation in the perinatal period. These studies show that the cerebral vessels are remarkably sensitive to high oxygen, and concentrations no higher than those commonly used therapeutically for premature infants and newborn term infants with cardiac or respiratory diseases cause as much as 35% reductions in blood flow in most parts of the brain. Dr. Grave has found that these effects of oxygen are also associated with impairments of growth, nucleic acid synthesis, and cellular proliferation in the brain. These results suggest that oxygen inhalation therapy should be used cautiously and not indiscriminately during the perinatal period

or it could lead to retarded brain development and other deleterious effects in the nervous system.

The initial studies in the development of a method for the simultaneous measurement of the rates of glucose utilization in all the component structures of the brain in the intact conscious animal have been carried out. Although such a method would be invaluable for relating function and metabolism in the CNS in various physiological, pharmacological, and pathological states, no such method presently exists. The initial studies are extremely promising. The values thus far obtained in normal rats and cats are already very close to what might have been expected. The theoretical problems appear to be essentially solved, and only a few technical but soluble problems remain before the method can become a routine useful tool for neurochemical investigations.

Section on Myelin Chemistry
Marian W. Kies, Chief

During the past year, the research staff of the Section on Myelin Chemistry has made considerable progress in their investigations of the relationship between structure and activity of myelin basic protein (MyBP) and the mechanisms involved in the pathogenesis of experimental allergic encephalomyelitis (EAE). Chemical studies on MyBP have been directed toward three more or less independent goals: a) characterization of charge heterogeneity; b) identification of trace contaminants; and c) delineation of species interrelationships among certain non-mammalian and the more commonly studied mammalian MyBPs.

a. Microheterogeneity—Six components of MyBP have been obtained by Mrs. Deibler through chromatography of purified guinea pig MyBP on carboxymethylcellulose. All have been found to be highly encephalitogenic and presumably equivalent in biological activity. The amino acid residues in the individual components are essentially identical except for minor differences possibly arising from trace contaminants. Electrophoresis at high pH confirms the fact that we have achieved good separation of five components each free of the neighboring ones. The separated components when mixed together yield an electrophoretic pattern essentially identical to that of the total basic protein from which they were prepared.

Enzymatic studies have shown that the MyBPs, like the histones, are remarkably susceptible to various alterations by enzymes present in the soluble supernatant fraction of brain homogenate. The purified protein can be methylated or phosphorylated by the crude soluble enzyme mixture.

Our preliminary results indicate, however, that neither methylation nor phosphorylation is the primary source of charge heterogeneity in vivo. A third possible enzymatic mechanism for inducing this phenomenon is deamidation. Studies on this reaction are now underway.

b. Identification of probable contaminants of purified myelin basic proteins—Although purified MyBP was originally believed to be homogeneous, we now know from immunochemical data that highly antigenic contaminants accompany myelin basic proteins through practically every purification step. Improved electrophoretic and chromatographic techniques have permitted characterization of some of these proteins in our preparations of MyBPs. One of the proteins which accompany BP through various purification steps is lysine-rich histone. We have recently isolated and identified this histone in MyBP preparations. A second contaminant is a slightly basic non-histone protein present also in liver, while the third is a highly basic CNS-specific protein that is very similar to BP in charge but is considerably larger in size. Recognition and removal of these contaminants is extremely important because of the potential use of MyBP for immunologic studies on cells and sera of neurologic patients.

c. Species interrelationships—Last year we reported that rat myelin basic proteins were different from guinea pig in that they occurred in two different molecular sizes in rat CNS. We have now shown that mouse and hamster, both members of the same rodent suborder as rats (Myomorpha) have two MyBPs. Prairie dog, woodchuck, and squirrel (suborder Sciuromorpha) also have two myelin basic proteins. In contrast, a single myelin basic protein was found to be characteristic of members of the third suborder, Hystricomorpha—guinea pig and chinchilla.

Amino acid analysis coupled with gel filtration studies of the two rat proteins provided evidence that these two proteins differ by about 40 amino acid residues. Amino acid analyses of the larger rat protein also indicated its marked similarity to bovine and human myelin basic proteins which have been sequenced by other investigators. By analogy with this published information, we have been able to predict the location and nature of the polypeptide segment which is present in the large molecule but absent in the small. Analysis of tryptic digests and bioassay of the two proteins (large and small) have confirmed our predictions of the nature of the deletion. Although the deletion does not prevent the small protein from functioning satisfactorily as a structural protein of myelin, it does markedly depress its encephalitogenic activity in guinea pigs but not Lewis rats.

Myelin BPs have also been isolated from CNS tissue of chicken, turtle, frog, carp, and shark. The chicken and turtle proteins were non-encephalitogenic in guinea pigs but were active in Lewis rats. We are beginning to understand some of the reasons for the conflicting data which have been reported on the encephalitogenicity of various MyBPs. Guinea pigs, rats, monkeys, and rabbits have been used for bioassay with apparently inconsistent results. It is now evident that there are multiple encephalitogenic sites in these proteins which do not have equivalent activities in all species. Slight variations in structure have resulted in marked variations in activity.

Section on Membrane Chemistry
Louis Sokoloff, Acting Chief

A number of laboratories, including this Section, have observed that acetylcholine stimulates phosphate incorporation into phosphatidylinositol in preparations from neural tissues. It has been commonly believed that this effect reflects the specific action of acetylcholine at the receptor site on the membrane of the effector cell. Recent studies in this Section have raised doubts about this conclusion. Acetylcholine has been found to have no such effects in normal or denervated diaphragm, muscle tissue which is acetylcholine-sensitive. Denervation, which deprives the muscle of its normal acetylcholine stimulus, was found to have reduced phosphate incorporation into phosphatidylinositol, but this decrease was found to be nearly as great in areas of tissue devoid of acetylcholine receptors as in areas which contain the end-plates. Studies recently carried out, and still in progress, strongly indicate that the phosphatidylinositol turn-over may be Ca^{++}-dependent. EGTA, a potent Ca^{++}-binding agent, markedly inhibits the incorporation of phosphate into phosphatidylinositol in muscle preparations. Since free Ca^{++} is believed to be intimately related to the coupling of excitation and contraction in muscle, these results suggest that phosphoinositides may be involved in the mechanism of this important coupling process.

Annual Report of the

Laboratory of General and Comparative Biochemistry

National Institute of Mental Health

Giulio L. Cantoni, Chief

The research program of the Laboratory has developed more favorably in the current year than in the previous one. However, we still suffer greatly from the drastic reduction in scientific manpower that has practically halved the strength of the Laboratory. We continue to exert every effort to remedy, in part at least, this situation through use of guest workers (supported by outside fellowships) and collaboration with other groups at N.I.H. and elsewhere, but difficulties and less than optimal overall performance is likely to continue until we can strengthen the Laboratory.

The focus of the research program of the Section on Alkaloid Biosynthesis continues to be the metabolism of sulfur containing amino acid. The work can be divided into two principal lines of investigation: a) transulfuration and methionine biosynthesis in plants; and b) metabolism of methionine in man with special emphasis on homocystinuria.

The most notable development during the past year has been the emergence of a preliminary understanding of the steps by which methionine may be formed by higher plants. Studies of this problem were initiated several years ago because of the importance of methionine as a limiting factor in the nutritional value of many plant food materials. At that time, methionine biosynthesis by any biological form was not clearly understood. It has now become clear that bacteria and molds form methionine by steps which differ in the two taxa. This unusual situation lends further comparative biochemical interest to the study of methionine biosynthesis in higher plants.

The earlier results of Drs. Mudd and Giovanelli demonstrated the importance of activation of the hydroxyl group of homoserine prior to conversion of this amino acid to homocysteine. An enzyme was detected in plants which could form homocysteine (and methionine) directly from O-acetylhomoserine. Alternatively, enzymes were demonstrated which could convert O-oxalyl, O-malonyl, or O-succinyl-homoserine to cystathionine, and the latter to homocysteine. Two problems remained. Was homocysteine formed by the direct pathway, or was cystathionine an important intermediate? If the latter, which O-alkyl-homoserine was the physiologically important one?

To answer these questions, attempts were made to study the enzymic formation of the O-alkylated homoserine derivatives. The results were surprising and somewhat disappointing. No gnerally distributed plant enzyme has been detected which catalyzes the formation of any of these O-alkyl compounds. Thus, neither of the two suggested pathways of methionine formation appeared to be feasible. A way out of this dilemma has very recently become apparent. Plants have enzymes not only to form phosphohomoserine but also to convert this activated derivative to cystathionine. These reactions permit postulation of a pathway for methionine synthesis. It will be of great interest to attempt to establish the existence of this unique pathway by more definitive experiments and to determine the range of organisms which utilize it. Once these goals are accomplished it will be possible to investigate in a meaningful way the regulation of methionine biosynthesis and to seek means to induce plants to form more of this essential and limiting nutrient.

The second major project in this Section continues to be the investigation of transsulfuration in mammals, chiefly through the study of mutants affecting this process. During the past year investigations of patients with abnormalities of B_{12} metabolism have been extended in two directions: (a) Two cases which appear to be very similar to the original case described last year have been discovered and studied. It appears that these siblings are able to accumulate neither of the two known coenzymatically active derivatives of B_{12}. It is striking that these children are not severely ill, affording an opportunity to perform studies upon them which otherwise would be impossible. These patients also point up a major question about B_{12} function. Why do they not have pernicious anemia? No reason for the lack of pernicious anemia can be advanced which is in accord with current concepts of the pathophysiology of pernicious anemia? It is to be expected, then, that solution of this quandry will alter our understanding of B_{12} function in the mammal. (b) Study of a patient with B_{12}-responsive methylmalonic aciduria, but normal homocysteine metabolism, has shown that it is possible to lack the ability to form deoxyadenosyl-B_{12}, while at the same time retaining the capacity to form methyl-B_{12} . Establishment of this point clarifies the probable pathway of mammalian B_{12} metabolism. It is to be hoped that further studies of these and similar patients will continue to throw light upon mammalian B_{12} metabolism.

The studies of cystathionine synthase deficient cells show promise of indicating the basic genetic and biochemical difference between vitamin B_6 (i.e. pyridoxine) responsive patients and those who do not so respond. As indicated in the individual project report, the general area of vitamin responsiveness is now attracting a good deal of attention among those interested in genetic diseases. Understanding of the various mechanisms which lead to

vitamin responsiveness will be important not only to further our knowledge of the relationships between cofactors and enzymes, but also to rationalize treatment of patients who show this responsiveness.

Finally, a substantial portion of time was devoted last year to the writing of a review "Biochemical Mechanisms in Methyl Group Transfer." It is, of course, to be hoped that this review will be useful to those interested in biological transmethylation.

It is of interest to note that a series of investigations devoted primarily to the elucidation of the biochemical pathways in methionine metabolism in various taxa is contributing information that is very relevant to two broader problems of great importance in the more general field of biomedical and behavioral sciences. Rice, wheat, and corn supply the principal sources of amino acids and proteins for the bulk of the undernourished population of the world. These foods are not nutritionally complete since they have very low methionine and lysine content. Knowledge of the pathways and mechanisms of methionine biosynthesis and its control in plants might open the way to the development and selection of a series of biochemical mutants capable of accumulating larger amounts of methionine in proteins or as free amino acid and might, therefore, provide an important route to the eventual elimination of protein deficiency in the nutrition of literally hundreds of millions of people.

The studies on homocystinuria are relevant to mental retardation, one of the principal target areas of interest to NIMH. Homocystinuria is, with phenylketonuria, the most frequent cause of mental retardation. Our investigations have demonstrated that through dietary manipulation it may be possible to raise the level activity of cystathionine synthase and thus to relieve at least partially the biochemical block that is responsible for the clinical manifestation of the disease. There is every reason to expect that in a number of cases significant therapeutic benefits may be forthcoming through this approach.

Another project of the LGCB is relevant to the etiology and management of mental retardation. Merril's work shows that a bacterial virus, the bacteriophage λpGal, can be introduced into human cells and express its biological activity. The bacteriophage induces in E. coli the formation of enzymes necessary for the metabolism of galactose: one of these enzymes, galactose transferase, is missing from the cells of patients suffering from galactosemia, a genetic disease often associated with mental retardation. Merril has shown that galactose transferase activity can be demonstrated in the cells from a galactosemic patient after the introduction in these cells the bacteriophage λpGal. While it is not yet known whether transferase production is the result of integration of the viral DNA into the host genome or whether

the viral DNA is functioning independently in the cytoplasm in a plasmid-like fashion, the results are of great interest both at a purely theoretical and fundamental level and at a more "applied" level as a possible model for "gene therapy."

Dr. Klee has continued to study the important biological problem of protein structure conformation. Proteins in solution exist in only one or a relatively small number of conformations and it has been evident for some time that the primary, genetically determined, amino acid sequence in a polypeptide chain folds in specific ways to reach the three dimensional conformation of a native protein.

The conformational properties of a number of peptide fragments of ribonuclease and of insulin were studied in the past year with results which are in accord with predictions made on the basis of his earlier work. Namely, those portions of the polypeptide chain which are known to exist in helical regions in the intact protein participate in a helix-like structure in solution as well. The highly flexible structures found in such peptides may profitably be distinguished from fully formed helices in completed proteins by considering them to be "nascent helices." In the insulin B chain, a nascent helix which is more stable at 37° than at 0° has been discovered. On the other hand, the nascent helix at the amino terminus of ribonuclease is more stable at low temperatures than high. Thus, there would appear to be at least two qualitatively different ways in which helical structures are determined.

Dr. Klee's recent work with the lactose synthetase system has shown that α-lactalbumin exerts its modifying influence on the specificity of the A-protein by formation of a 1:1 molecular complex, in the presence of the substrates of the enzyme. The nature of the complex was studied by a number of methods but most definitively by the application of a newly developed method of band sedimentation in the analytical ultracentrifuge. With this method the sedimentation and binding properties of a zone of A-protein (containing as little as 3 μg of enzyme) can be followed in the presence of varying amounts of α-lactalbumin and other componants of the system. The Klee's showed previously that α-lactalbumin increases the affinity of the A-protein for both types of acceptor sugars and that the change in specificity observed is a consequence of this increased binding affinity. Since substrates are required for the binding of α-lactalbumin to the A-protein the enhanced affinity of substrates in the presence of α-lactalbumin can be considered to be a direct result of complex formation by virtue of the law of mass action. The lactose synthetase system represents a novel type of evolutionary adaptation in which an enzyme which serves an important role in glycoprotein and glycolipid biosynthesis (the A-protein is modified to accomplish a new function, lactose biosynthesis, by complexing

with another, non-catalytic, protein. The system is a clear example of how protein function can be modified in a dramatic way by the formation of a more complex structure.

My own group has continued to study the first step of protein synthesis, namely the activation of amino acids by the aminoacyl tRNA synthetases and the structure of the cognate tRNA. Our work on the serine tRNA synthetase from E. coli has progressed satisfactorily. In spite of their central importance in the biology of the cell these enzymes have received only limited attention and very little is known about their structure and the molecular basis for the ability of these enzymes to recognize with a high degree of specificity their substrates, namely the amino acids and tRNAs.

We have initiated a new investigation on an enzyme that could turn out to be very interesting and important: a ribonuclease that appears to be specific for the RNA moiety of a RNA-DNA hybrid. Not much is known about the occurrence of RNA-DNA hybrids in normal cell functioning. It has been discovered in the last few months that cellular mechanisms exist for "reserve" information transfer from RNA to DNA and it is postulated that RNA-DNA hybrids are formed as intermediates in this process. The biological function of ribonuclease H (for hybrid) could be related to this process. The significance of this novel mechanism of information transfer in biology is not known. At first it was assumed that this process was important only in the mechanism of infection by tumor producing RNA viruses, but more recent discoveries seem to indicate a broader function. Ribonuclease H could be an important, perhaps an essential component of this process and studies of its specificity, cellular distribution and mechanism of action are clearly indicated.

Annual Report of the Laboratory of Neurobiology

National Institute of Mental Health

Ichiji Tasaki, Chief

The nervous system is being studied in the Laboratory of Neurobiology through experiments on the molecular structure of the nerve cell membrane, experiments on the metabolic activity of proteins in brain cell nuclei, and experiments on the relations between cells in the visual system of the brain and behavior.

The macromolecular structure of the nerve cell membrane and the change in that structure during the action potential are being studied by Dr. Ichiji Tasaki, Dr. Akira Watanabe, Dr. Mark Hallett and Mr. Ronald Sandlin. They are investigating the phenomenon of extrinsic fluorescence of nerve using techniques first developed in this laboratory. Over the past year the investigation has been devoted to analysis of fluorescent signals obtained with the hydrophobic probe dyes in squid giant axons. The fluorescent light from the axon which diminished during the action potential has been shown to be coming from a special class of dye molecules in the axon which are presumed to be incorporated in the membrane. From the properties of this fluorescent light it can be deduced that the membrane in the resting state has a highly ordered crystalline structure of a hydrophobic nature. During the action potential the membrane conductance increases and this is probably associated with a hydrophobic-hydrophilic transition of the membrane.

The metabolic activities of proteins in nuclei from brain cells and their relation to sensory stimulation and DNA replication in the brain are being investigated by Dr. Jose Burdman. Experiments are performed *in vitro* by incubating nuclei isolated from brain cells with a radioactive amino acid and *in vivo* after the injection of a radioactive amino acid. The *in vitro* experiments indicate that there are several sites of protein synthesis in nuclei from brain cells. *In vivo*, stimulation with flashing light does not result in any significant change in the rate of synthesis of nuclear proteins in the visual cortex. During post-natal development of the brain, the rate of cell division reaches a peak at about the 8th day after birth. The rate of synthesis of DNA associated proteins in the brain parallels the rate of DNA synthesis. This is not the case with other nuclear proteins which are not associated with the DNA, such as those of the nuclear sap and nucleolar proteins. This might be important in explaining the sequence of events occurring intracellularly and leading to mitosis or suppression of mitosis.

The problem of how the brain processes visual information is being studied by Dr. Robert Wurtz and Dr. Michael Goldberg. Using monkeys which are trained to do a visual task, they have studied cells in one branch of the visual system, the superior colliculus. The majority of cells in the upper layers of the superior colliculus have receptive fields which do not require a very specific visual stimulus: any position within a large area, any direction of the movement, or any shape or orientation, will be effective as stimulus. These cells would seem to have great value in determining that something is in a part of the visual field but not at all what it is. In addition, many of these same cells show an enhanced response when the monkey had to attend to the receptive field stimulus in order to make an eye movement to it. The attention effect usually does not significantly alter the receptive field of the cell but instead enhances the response of the cell to stimuli within the field. The net effect of this selective enhancement by attention is probably a more reliable transmission of information to higher levels of the nervous system.

Annual Report of the Laboratory of Neurochemistry

National Institute of Mental Health

Seymour Kaufman, Chief

One of the major efforts of the Laboratory of Neurochemistry continues to be the study of a group of hydroxylases that play key roles in the metabolism of the nervous system. These studies have two interdependent goals: a) to understand the mechanism of the reactions catalyzed by the enzymes and b) to gain insight into the manner in which these enzymes may be regulated in vivo. During the last year, progress toward both of these goals was realized.

With essentially pure phenylalanine hydroxylase from rat liver, it was found that the mechanism of the reaction is one which demands that all three substrates (phenylalanine, oxygen, and tetrahydropterin) be on the enzyme before any reaction occurs. This result rules out the possibility that a reduced enzyme intermediate is involved in the reaction and clearly distinguishes this mechanism from that of dopamine β-hydroxylase. With the latter enzyme, earlier studies from this laboratory provided strong evidence for just such an intermediate. The picture that is clearly emerging from these studies is that even within the group of hydroxylases, there is a diversity in the types of mechanisms that are operating.

It has also been found that phenylalanine hydroxylase is an iron-enzyme, the iron being essential for the catalytic functioning of the enzyme. Although the manner in which the iron participates in the hydroxylation reaction is not known, this is the first implication of this element in the biosynthetic pathway that leads from phenylalanine to the catecholamines, dopa, dopamine, norepinephrine and epinephrine. Based on the similiarity between phenylalanine and tyrosine hydroxylases, it can be predicted that the latter enzyme will also prove to be an iron-protein. Thus, iron may be added to the list of essential elements and coenzymes that have been shown in this laboratory to participate in catecholamine biosynthesis. That list now includes iron, copper, ascorbic acid and unconjugated pterins.

Our knowledge of the role in metabolism of the last named group of coenzymes was considerably refined by our recent results. Two naturally-occurring pterins, tetrahydrofolate and tetrahydrobiopterin have been shown to be able to function in vitro as hydroxylase coenzymes. A question of considerable importance that had remained unanswered until recently was, which of these two pterins fulfills this role in vivo? During the last year, we found that the major part of the hydroxylase coenzyme activity of tetrahydrofolate is due to its contamination with a highly active unconjugated pterin, 6-methyltetrahydropterin; tetrahydrofolate,

itself, has very low hydroxylase coenzyme activity. The answer to the question about the in vivo activity of tetrahydrofolate therefore has been provided quite indirectly, but still decisively: The hydroxylase coenzyme activity of pure tetrahydrofolate is too low to be of physiological significance.

An important example of how knowledge gained from studies of the properties of highly purified enzymes may provide clues to the in vivo regulation of the activity of these enzymes comes from our recent finding that oxygen is a potent inhibitor of purified phenylalanine hydroxylase. The inhibition is manifest in the presence of the naturally-occurring cofactor, tetrahydrobiopterin, but not in the presence of a synthetic analogue of the cofactor. If, as seems likely, this property is shared by the other pterin-hydroxylases, tyrosine and tryptophan hydroxylases, it can be predicted that norepinephrine and serotonin synthesis may be inhibited by excess oxygen. Inhibition of these hydroxylases may explain, in part, the known toxicity of oxygen in the nervous system.

A new aspect of the regulation of phenylalanine hydroxylase was investigated during the last year, i.e., the pattern of appearance of the enzyme in liver during fetal development. Two strikingly different patterns were found. In the rat, the enzyme is not present until the day before birth. Within less than a 24-hour period, the activity of the enzyme increases to the adult levels. There is also a coordinated increase in the levels of two other essential components of the hydroxylation system: dihydropteridine reductase and the pterin cofactor. By contrast, in the guinea pig and in the human, the hydroxylase is present during the second half of the gestation period. The presence of the enzyme in humans at this early time probably affords partial protection of the fetal nervous system from the toxic effects of excess phenylalanine. This may explain why non-phenylketonuric offspring from phenylketonuric mothers rarely suffer from severe mental retardation.

There were important advances during the last year in our understanding of the biochemistry of the process of integration of viral genes into the host genome. Previous work had established that integration required the presence of a phage-coded system called "Int". The presence of "Int" had been inferred from genetic data but its chemical and physical properties had never been studied. "Int" has now been partially purified and some of its physical properties, such as its molecular weight, have been established. These results represent an important start in the biochemical analysis of a problem that was heretofore the exclusive province of the geneticist.

In the Section on Physical Chemistry a new analytical technique was developed for the resolution of all protein and glycoprotein material in a cell membrane. With the use of this technique it has been possible to draw a very detailed profile of the protein subunit composition of membranes that is characteristic of different cells. For the rat liver cell, this technique combined with the use of iodine-tagged insulin, has led to the detection and identification of the insulin receptor in the cell membrane. This last result should facilitate a study of the biochemical nature of the defect in diabetes.

Annual Report of the Laboratory of Neurophysiology

National Institute of Mental Health

Edward V. Evarts, M.D., Chief

July 1, 1970 -- June 30, 1971

This summary of research project reports will be divided into four parts, corresponding to the research of the four senior scientists in the Laboratory.

I: Dr. David Carpenter's research has been concentrated in two areas of cellular neurophysiology. The first of these projects, entitled the ionic and metabolic basis of neuronal thermosensitivity has been undertaken to investigate the mechanisms which allow nerve cells to respond to changes of temperature and to compare the coding of thermal information in those neurons which mediate thermal sensation with that in those neurons not known to be involved in perception or regulation of temperature. It has been found that thermosensitivity is a general property of neurons in both vertebrates and invertebrates, and that this is so even for neurons which have no role in temperature perception. It has been concluded that thermosensitivity of a neuron does not necessarily indicate that this information is used by the nervous system.

Aspirin is a widely used antipyretic drug, and because of this it was decided to investigate the effect of aspirin on the membrane properties which underlie neuronal thermosensitivity and neuronal excitability in general. It seemed that the results of such investigations might be relevant not only to the antipyretic actions of aspirin but to its analgesic actions as well. It was found that salicylate decreases both the output from and the effectiveness of input to a neuron. This observation should provide a much needed background for further exploration in vertebrate preparations. It has also been found that the underlying ionic mechanisms consist of an increase in the cells' permeability to potassium coupled with a decrease in permeability to chloride. These latter findings are similar to those seen in vertebrate red cell membranes. It is possible that similar mechanisms are involved in salicylate's analgesic and antipyretic effects. These results should also provide a firm beginning for future research on the therapeutic actions of salicylate.

Direct examination of the metabolic basis of neuronal thermosensitivity has been carried out in certain large neurons of certain invertebrates (Aplysia and Navanax). In most excitable tissues studied to date, ion diffusion gradients and selective membrane permeability form the basis of neuronal function. The study of how temperature affects these parameters is therefore important as a general property of nerve cells. It is of special

interest in Aplysia neurons because of the fact that specific membrane resistance is much greater in this preparation than in many others. As a result, the membrane potential is much more sensitive to the small changes in g_{Na^+} caused by temperature changes. These experiments suggest that the results seen in Aplysia neurons as compared with the classical observations of squid axon may reflect a basic difference between neuronal cell bodies and axons.

A second major area of Dr. Carpenter's research has dealt with the state of ions and water in living cells. Results to date suggest that ions in nerve cell bodies exist in a very different state from those in axons. If this be true it is necessary to re-examine many of the concepts which were developed to explain electrical events in axons and which have been assumed to apply to all excitable tissues on the assumption that all ions are free. Moreover, it seems very possible that the state of ions in most cell bodies may be more like that in Aplysia neurons than that in red blood cells and squid axons since the cell bodies contain many more membraneous structures and a higher concentration of organic molecules (which are probably the site of the ion and water binding). These observations, therefore, may have relevance to all types of cells.

II. Dr. Edward Evarts' research has dealt with the functional organization of the brain in the initiation and control of voluntary movement. The objective of this work is to discover what areas of the brain initiate movement, what areas control and regulate movement, and how these areas for initiation and control are interrelated. In connection with this project a number of different cerebral areas have been investigated. To further understand the role of the basal ganglia in motor function, an experiment was carried out to determine whether neuronal activity in the basal ganglia precedes or follows the onset of movement. Monkeys were trained to grasp an immovable rod and steadily push or pull, and then to rapidly reverse the direction of the force at the presentation of a visual stimulus. Extracellular recordings were made from neurons in the contralateral putamen and pallidum during repeated sequences of movement. Numerous units in both the putamen and pallidum showed increases or decreases in activity prior to the onset of movement. Related units frequently exhibited different levels of activity during maintained pushing and pulling and in relation to the transient shift between the two steady states. These changes in activity prior to movement indicate that the basal ganglia play a role in the initiation of movement. Since the major efferent projections of the pallidum are to the ventroanterior and ventrolateral nuclei of the thalamus, which in turn project upon the precentral cortex, it would seem that the output from the basal ganglia may influence the activity of the motor cortex prior to the onset of movement.

This work on the extrapyramidal system is of special interest in relation to mental health research because it seems to lie somewhere between a purely motor structure and a higher level integrating center. Thus, lesions and disturbances of the extrapyramidal system result not only in abnormal

movement but also in certain modifications of intellectual and psychic function. Patients with Parkinsonism, for instance, not only have disturbed movements but also show alterations of affect. In addition, there are certain extrapyramidal syndromes associated with mental deficiency (e.g., Huntington's Chorea). It seems clear that an understanding of the way in which the neurons of the extrapyramidal system function will provide important clues as to a number of presently unknown basic mechanisms of mental function.

Studies have also been carried out on the cerebellum. In these studies, action potentials of cerebellar Purkinje cells were observed in intact monkeys during sleep and waking. Purkinje cells exhibit two sorts of action potentials, called simple and complex spikes, and these two sorts of spikes were differently affected by sleep. Simple-spike activity (generated by the parallel fiber inputs to the Purkinje cell) was highest during sleep with rapid eye movements as compared with both waking and sleep with electroencephalographic slow waves. In contrast, complex-spike activity (generated by the climbing fiber inputs to the Purkinje cell) was lowest during sleep with rapid eye movements. The complex action potential of the Purkinje cell consists of an initial large spike followed by one or more smaller secondary spikes, and the number of these secondary spikes was found to be independent of the background discharge frequency of the simple spike. This independence suggests a possible role of presynaptic factors rather than the excitability level of the Purkinje cell itself in determining the number of secondary discharges occurring in the complex spike.

The third area of investigation on motor control mechanisms has dealt with activity of postcentral sensory cortex neurons in association with movement. In previous studies neurons in the precentral motor cortex were found to discharge as much as 100 msec prior to movement. But what of neurons outside this motor area? Is discharge prior to movement restricted to the "motor" division of the sensorimotor cortex, or does such discharge occur in the postcentral "sensory" division as well? Muscular contraction can be elicited by electrical stimulation of postcentral as well as precentral cortex, and the existence of peripheral sensory inputs to postcentral neurons should not obscure the fact that postcentral neurons received powerful inputs from non-sensory areas of the brain. To determine the relation between timing of discharge in precentral motor and postcentral sensory cortex, recordings were obtained (in the same monkey) from pre- and postcentral hand areas in association with reaction time performance. The results showed that postcentral activity follows movement initiation (presumably as a result of feedback from the periphery). Thus, recordings in moving animals reveal a striking functional differentiation within the sensorimotor cortex: precentral activity precedes and initiates movement, whereas postcentral activity follows movement and depends on feedback from the periphery.

III. Dr. Paul MacLean's research has dealt with limbic integration and behavior, with studies on the functions of the limbic system and of the striatal complex. The mammalian striatal complex (corpus striatum + globus pallidus) reflects the pattern of organization of a major part of the reptilian forebrain, whereas the limbic system (limbic cortex + its primary nuclear connections) is largely a paleomammalian derivative.

The preliminary findings of a microelectrode study on visceral inputs to the limbic cortex indicate that the majority of units in the middle segment of the cingulate gyrus can be regularly excited by vagal stimulation, with latencies ranging from 10-40 msec. These observations promise to contribute to the knowledge of sensory mechanisms involved in the cortical regulation of visceral functions. It is known, for example, that stimulation of parts of the cingulate cortex elicit autonomic effects, including cardiovascular and respiratory changes, and that ablations may interfere with hoarding and maternal functions. Clinically, anterior cingulomotomy has been claimed to prevent withdrawal symptoms in individuals addicted to narcotic drugs.

In further experiments on the anatomical projects of the archicortex it has been shown for the first time in a primate that some fibers of the fornix reach the tuber cinereum. This new finding is of interest in view of the reported suppression of the secretion of ACTH by the pituitary gland following hippocampal stimulation.

As regards neural mechanisms of genetically constituted forms of behavior, it has been found that symmetrical bilateral lesions of the anterior two-thirds of the cingulate gyri interfere with the expression of innate display behavior in the squirrel monkey. A topographic and volumetric analysis of lesions of the globus pallidus indicates that destruction of the posterior part of this structure is more effective than anterior damage in interfering with the innate display.

The chemistry of the corpus striatum is distinctive because of the very high content of acetylcholinesterase and of dopamine, whereas the parts of the limbic system are chemically of interest because of a high content of acetylcholine, 5-hydroxytryptamine (serotonin), and norepinephrine. The Section's studies on biogenic amines have dealt with three questions of current interest: (1) It has been reported that in schizophrenia exacerbation of symptoms may be associated with a rise in urinary tryptamine, a provocative finding in the light of the body's capacity to metabolize tryptamine into dimethyltryptamine, a psychotogenic substance. Experiments conducted in this Section have shown that a highly purified form of tryptamine will produce catatonia in squirrel monkeys and that 5-hydroxytryptophan, a precursor of serotonin, induces a prolonged catalepsy, characterized by the animal's maintenance of bizarre postures and an increase in muscle tone. (2) It is believed that 6-hydroxydopamine (6-OHDA) damages neurons containing norepinephrine and dopamine. In the squirrel monkey the intraventricular administration of 6-OHDA followed by treatment with L-dopa or apomorphine

results in dyskinesias. These findings may help to shed some light on the dyskinesias complicating the treatment of Parkinson's disease with L-dopa. (3) As in other species, it has been found that intraventricular norepinephrine (doses ranging from 50 µg to 1 mg) have a sedative effect on the squirrel monkey. Such findings do not seem to be in harmony with the clinical theory that mania is due to an excess of cerebral norepinephrine.

In the past, the study of the role of olfaction in the behavior of animals has lagged because of inadequate apparatus for presenting olfactory cues. A new type of olfactometer is being perfected in this Section that appears to eliminate the shortcomings of earlier devices. It will be used to investigate neural structures involved in the detection and discrimination of odors, as well as to test the incentive value of a variety of natural odors and pheromones. Preliminary control experiments have shown that the rat makes better use of olfactory than auditory information in solving a specific problem and that a reversal learning set is acquired much more quickly when odor cues are employed. These findings call for a reevaluation of generalizations about problem-solving abilities in rats that have been based on experiments using non-olfactory cues.

IV. Dr. Stanley Rapoport's work has been concentrated on two major topics. The first of these concerned the electrical, ionic and physical properties of muscle. This project is designed (a) to determine the elastic and plastic properties of the muscle fiber membrane (sarcolemma) and relate them to the physiological function of the fiber under conditions of tension; (b) to determine the factors controlling the size and electrical characteristics of the transverse tubular system (T system) in muscle fibers and to relate properties of the transverse tubular system to excitation-contraction coupling and the electrical properties of the muscle fiber. The project has provided knowledge of the mechanical properties of the sarcolemma and myofibrils, and of their relative contribution to tension as a function of stretch. This knowledge is necessary to understand the process of contraction and of the resistance of the muscle to stretch under physiological conditions. Correlation between electromicroscopic structure of the sarcolemma and myofibrils and their properties permits a better understanding of the molecular forces regulating tension.

The transverse tubular system is thought to be the pathway for the flow of current between the inside and outside of the muscle fiber, and thus necessary for the coupling between the electrical events at the surface of the cell and the mechanical events within the cell. In order to explain the coupling in detail, it is necessary to know the electrical and physical properties of the tubules. This project is a continuation of a previous study which proposed that the transverse tubular system contains fixed charges which participate in the regulation of excitation-concentration coupling.

The second major area of Dr. Rapoport's work has dealt with transport mechanisms across membranes. This project is designed to consider and

amplify the theory of transport of substances across artificial and cellular membranes, and to relate transport to membrane potential and function. In studies on a model of the Na-K exchange pump, a theory was developed which relates, for the first time, metabolic rate and stoichiometry of the active transport reaction to the neurophysiological parameters of membrane potential, hyperpolarization, membrane resistance and ionic currents. Data which previously were incompletely interpreted on the electrogenic pump in muscle were shown to fit into the model. The model should therefore be applicable to a variety of nervous and muscle tissues and proposes for the first time feedback relations between metabolic activity and nervous function.

Another set of experiments succeeded in developing a new model for the blood-brain barrier. This model proposes that the barrier can be broken down irreversibly, as it has in the past, or reversibly, by shrinkage of possible endothelium cells, because of osmotic action. The reversible breakdown of the barrier could be of significance to the treatment of cerebral diseases by facilitating drug passage, as well as to the treatment and understanding of cerebral edema.

Additional work has been done on passive and active transport among fetal compartments of the sheep. The model and analysis of fetal transport are important to the understanding of general transport mechansims as well as the fetal-maternal relation during gestation.

The final aspect of Dr. Rapoport's work on transport mechanisms across membranes has dealt with theoretical analysis of net tracer flux due to volume circulation in a membrane with pores of different sizes. The model developed as a result of this work clarifies one of the problems in interpreting the phenomenological coefficients in biological and artificial membranes. The solute-solute interaction model had been proposed for active transport in biological membranes such as toad skin and, in view of the new interpretation, it is hoped that the biological data can be reevaluated.

Annual Report of the Section on Technical Development

National Institute of Mental Health

National Institute of Neurological Diseases and Stroke

July 1, 1970 - June 30, 1971

James S. Bryan, Chief

During the past 12 months, the Section on Technical Development continued to fulfill its traditional role of support of NIMH and NINDS research efforts. Continuing assistance was made available in shop help, special purpose instruments, instrumentation systems, and assistance in computer oriented research and digital instrumentation.

The major load on the Section in the past year has been the check-out, acceptance and custom interface fabrication associated with the NIMH Building 10 on-line computer system (Systems Engineering Laboratories 810B) which was installed July 23, 1970 and accepted on August 23, 1970. Hardware design and fabrication for the system, although far from complete, is now beginning to taper off and the major remaining effort will lie in the area of software support for new users. Usage of this equipment has thus far been limited to software development and a few small batch applications. Scheduled on-line use is expected to begin in May 1971.

Appendix II shows a breakdown by Laboratory of the usage of the three small laboratory-type computers maintained and supported by the Section. All of this equipment is now loaded near capacity.

Staff changes involved the addition of one electronic technician, a systems programmer for the 810B and the loss of our two part-time student assistants.

Appendix I shows a breakdown of section activity by laboratory. As usual, almost all research within the section has involved collaboration with laboratories in NIMH and NINDS and is, therefore, reported as part of the projects in the laboratories involved. Exceptions to the foregoing include a small but continuing effort in neural modeling, and development of equipment to investigate the nature of motor deficits in patients with dystonia or Parkinson's disease.

Our most recent neural modeling effort has involved the development in collaboration with the Laboratory of Applied Studies, DCRT, of a model neuron with a multi-compartment dendritic network capable of simulating nonlinear spatial summation. Future work will involve the application of this neuron in collaboration with the Laboratory of Neurophysiology, NINDS, to model the responses of ganglion cells in turtle retina. The intent is to define the role of the horizontal cells in vision.

The equipment to measure motor deficits involves a device which has been built to measure angular velocity while applying steps and pulses of torque to the elbow joint both when resting and during voluntary motion. The intent is to measure the properties of the postural and motional motor control loops with the eventual goal of relating the derived parameters to disease states, and use in evaluating surgery, drugs, and physical therapy. These later steps will involve collaboration with the Section on Experimental Therapeutics, Laboratory of Clinical Science, NIMH and the Surgical Neurology Branch, NINDS.

A total of 199 projects were completed in the last year. A full review of all of them would be too lengthy; however, a summary list of some of the more important ones follows.

PROJECTS COMPLETED

PROJECT	REQUESTOR
Oscillator with voltage control of amplitude and frequency	Dr. H. Funkenstein
Tester for watches as motion integrators	Dr. R. Bell
Neural spike window discriminators	Dr. M. Weiderhold Dr. P. Winter Dr. J.K. Penry
Speech gating and integrating system	Dr. D. Boomer
Antenna switching and frequency tracking systems for field and laboratory	Dr. F. Snyder
Logarithm of inter-spike interval converter	Dr. E. Schwartz
Nanoampere current sensor for microelectrode application	Dr. G. Fishbach
Microtome modification	Dr. E. Freese
3 level trapezoid waveform generator	Dr. G. Murray
EEG Calibrator, Models 1, 2, and 3	Dr. E. F. MacNichol,Jr.
Oscilloscope intensifier circuits	Dr. E. Evarts Dr. R. Wurtz
Rat colony data acquisition system modification, Phase I	Dr. J. Calhoun
Various chambers, baths, electrode holders and jigs	
Dr. W. Marshall	Dr. P. Winter
Dr. H. Nash	Dr. D. Carpenter
Dr. J. Heuser	Dr. D. Rottenberg
Dr. S. Rapoport	Dr. H. Latorre
Dr. E. Schmidt	Dr. R. Burke
Dr. F. Snyder	Dr. E. Freese
Dr. J. Newman	Dr. J. Warmholts
Dr. H. Levitan	Dr. D. Gilbert
Dr. W. Klee	Dr. M. Kies
Dr. R. Weinshilboum	Dr. M. Weiderhold
Dr. E. Evarts	Mr. L. Binstock
Dr. E. Schwartz	Dr. H. Webster

PROJECTS IN PROCESS

PROJECT	REQUESTOR
SEL 810B interface for HEPP board and display	Dr. E. Jerome
Electronics for rapid scanning microspectrophotometer	Dr. G. Murray
Slip ring cable assembly for unrestrained animal EEG	Dr. F. Snyder
Microelectrode amplifier Model 68A1	Dr. E.F. MacNichol, Jr. Dr. H. Wagner Dr. M. Fuortes Dr. K.C. Cole
Trial signalling apparatus for family testing	Dr. D. Reiss
SEL 810B multiple input-output interface	Dr. V. Carlson
EEG epileptiform spike detector	Dr. M. O'Connor
EEG amplifiers	Dr. F. Snyder Dr. D. Pfefferbaum
Auditory stimulus control panel	Dr. J. Newman
Rat treadmill exerciser	Dr. C. Jablecki
EEG calibrator M3 (eight units)	Dr. E.F. MacNichol, Jr.
810B interrupt terminal electronics	Dr. M. Buchsbaum
Rat colony data acquisition system modification, Phase II	Dr. J. Calhoun
Logarithm of interspike interval converter	Dr. W. Stell
Spring loaded peek-a-boo faces for infant testing apparatus	Dr. A. Caron
Various chambers, baths, electrode holders and jigs	

Dr. D. Gilbert	Dr. H. Latorre
Mr. L. Binstock	Dr. H. Webster
Dr. J. Newman	Dr. M. Weiderhold
Dr. K. Frank	Dr. Z. Wollberg
Dr. D. Fisher	

SECTION ON TECHNICAL DEVELOPMENT PROJECTS
--PROJECTS INITIATED WITHIN THE SECTION--

PROJECT	STATUS
Communication channel classic LINC to SEL 810B	In process
Multiple output vector display with character generator for SEL 810B	In process
PDP-12 IBM-compatible Mag tape interface	In process
Neural models of the cochlear nucleus	Complete
Multi-compartment neuron model	Complete
Device to measure motor deficits of Parkinson's patients	In process

APPENDIX I

Apportionment of Effort

ENGINEERING AND FABRICATION TIME

MAJOR USERS

LABORATORY OR BRANCH	HOURS	PERCENT
NIMH Computer, IR, DCBR, NIMH (including programmer)	8757	31.63
Psychology, NIMH	4885	17.64
Neurophysiology, NINDS	1911	6.90
Behavioral Biology, NICHD	1779	6.43
Biophysics, NINDS	1708	6.17
Clinical Psychobiology, NIMH	1387	5.01
Technical Development, NIMH-NINDS	1142	4.12
Office of the Director, NINDS	1060	3.83
Electroencephalography, NINDS	896	3.24

LABORATORY OR BRANCH	HOURS	PERCENT
Neurophysiology, NIMH	762	2.75
Adult Psychiatry, NIMH	736	2.65
Child Research, NIMH	647	2.34
Experimental Neurology, NINDS	448	1.61
Division of Special Mental Health Research, NIMH	260	.94
Clinical Science, NIMH	222	.80
Medical Neurology, NINDS	204	.74
Cerebral Metabolism, NIMH	182	.65
Neuropathology & Neuroanatomical Sciences, NINDS	157	.57
Neural Control, NINDS	145	.52
Neurochemistry, NINDS	110	.40
All other NIMH Labs	176	.64
All other NINDS Labs	112	.40
NIMH (Total)	18,014	67.9
NINDS (Total)	6,751	25.4
NICHD (Total)	1,779	6.7
TOTAL*	26,544	100.0

*Not included in the foregoing totals or in the breakdown by laboratory are 1982 hours spent in routine and computer maintenance internal to the Section, and the time of the Section Chief. Totals and percentage figures do not include time charged to the Section on Technical Development.

APPENDIX II

Laboratory Computer Utilization

Classic LINC	2996 hours
MicroLINC	2060 hours
PDP-12	1770 hours

LABORATORY OR BRANCH	LINC %	μLINC %	PDP-12 %	Total %
Overhead	.5	6.0	2.0	2.5
Psychology, NIMH	45.5	--	10.0	23.0
Technical Development, NIMH	--	3.0	4.5	2.0
Adult Psychiatry, NIMH	45.0	1.0	13.0	23.0
Socio-environmental Studies,NIMH	2.0	--	--	1.0
Neurophysiology, NIMH	--	40.0	3.0	13.0
Clinical Psychobiology, NIMH	3.0	--	0.5	1.5
Neural Control, NINDS	--	8.0	3.0	3.5
Biophysics, NINDS	--	25.0	3.0	8.0
Surgical Neurology, NINDS	4.0	--	--	1.5
Neurophysiology, NINDS	--	--	43.5	11.0
Electroencephalography, NINDS	--	--	3.5	1.0
Collaborative & Field Research,NINDS	--	--	13.0	3.5
Behavioral Biology, NICHD	--	17.0	.5	5.5
Physical Biology, NIAMD	--	--	.5	--
Total NIMH	96.0	46.5	32.0	65.0
Total NINDS	4.0	35.0	67.5	29.5
Total NICHD	--	18.5	0.5	5.5

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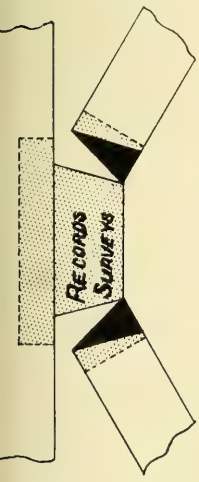

PART II

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NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1970 - June 30, 1971

VOLUME II

Individual Project Reports

ANNUAL REPORT
MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM -
Division of Clinical and Behavioral Research, and
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NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1970 - June 30, 1971

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Serial No. M-OD-CI-5(c)
1. Office of Director
2. Division of Clinical and Behavioral Research
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies in Schizophrenic Conditions: Psychosocial and Biological Interrelationships

Previous Serial Number: Same

Principal Investigator: David Shakow

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	1.50
Professional:	.90
Other:	.60

Project Description:

Objectives: To bring together a large body of experimental data on schizophrenia collected over several decades into a book (with attendant individual papers) which develops a theory of schizophrenia, particularly of the psychobiology of schizophrenia, centered around a concept of segmentalization. A detailed analysis of the body of experimental data already available from Worcester State Hospital studies and some new data gathered on our wards here and at St. Elizabeths will be used.

Methods Employed: In relation to the already accumulated materials in the area of physiology, psychophysiology and psychology the usual methods of statistical and conceptual analysis are used. Some parts of the relevant experimental literature will be utilized for further differentiation of the material. Related studies being carried out by other investigators in the Laboratory of Psychology and elsewhere in NIMH on schizophrenic, senescent and brain-damaged subjects will be used in these studies for control purposes.

Major Findings: During the year a major effort has gone into the further analysis and organization of data in the physiological, psychophysiological and psychological aspects of schizophrenia, with a view towards developing a unified theory of schizophrenia.

Significance to Bio-medical Research and the Program of the Institute: The studies mentioned above will contribute to the understanding of the phenomena of schizophrenia and eventually to a comprehensive theory of schizophrenia.

Proposed Course of Project: Continue further analysis of both published and still unpublished data, in the context of the analysis of relevant data from studies of others at NIH and elsewhere.

Publications:

Schizophrenia

Shakow, D.: The Worcester State Hospital Research on Schizophrenia. (Abbreviated Version.) To be published in a Festschrift volume for Dr. Roy R. Grinker, Sr., Fall 1971.

Shakow, D.: The Worcester State Hospital Research on Schizophrenia. (Complete version.) To be published as a monograph by the Journal of Abnormal Psychology, 1971.

Shakow, D.: Some Observations on the Psychology (and some fewer, on the Biology) of Schizophrenia. Paper presented at the Symposium on Schizophrenia, Leningrad, U.S.S.R., September 23-27, 1970. (Accepted for publication by the Journal of Nervous and Mental Diseases, 1971.) (To be published in somewhat abbreviated form by the D. Uznadze Institute of Psychology, Academy of Sciences of the Georgian S.S.R., Tbilisi, U.S.S.R. in January 1972.)

Shakow, D.: Discussion of Holzman's and Silverman's Contributions on Perception in Schizophrenia. (To be published in "Proceedings of the Conference of Schizophrenia: The Implications of Research Findings for Treatment and Teaching," held May 30-June 2, 1970, Fall, 1971.)

Psychotherapy

Shakow, D.: Patterns of Institutional Sponsorship. In R. R. Holt, (Ed.), New Horizons for Psychotherapy. New York: International Universities Press, 1971.

Medical Education

Shakow, D.: Conference on Psychiatric Education: The Contribution of Psychology in the Teaching of Psychiatry to Medical Students. Presented at the University of Rochester Conference on Medical Education in celebration of the Twenty-Fifth Anniversary of the Department of Psychiatry, Rochester, New York, March 30,31 and April 1, 1971. (To be published in the proceedings of the Conference, Fall 1971.)

Serial No. M-AP(C)-14-1
1. Adult Psychiatry Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Conceptualization and Dimensional Evaluation of Schizophrenia.

Principal Investigators: Lyman C. Wynne, M.D., Ph.D., Margaret T. Singer, Ph.D., and John Strauss, M.D.

Other Investigators: Helm Stierlin, M.D., Ph.D.; Winfield Scott, Ph.D.; Margaret Toohey; Dolf Pfefferbaum, M.D.; T. W. Carpenter, M.D.; Monte Buchsbaum, M.D. (Laboratory of Psychology); John Bartko, Ph.D. (Biometry Branch).

Cooperating Units: World Health Organization, Geneva, Switzerland; Spring Grove State Hospital, Maryland; Prince Georges County General Hospital; Laboratory of Psychology; Division of Computer Research and Technology, Biometry Branch.

Man Years (not included in cooperating projects):

Total:	.5
Professional:	.3
Other:	.2

Project Description:

Objectives: (1) This project aims to conceptualize major features of schizophrenic disorders along continua or dimensions in such a way that patients can be evaluated on the basis of data obtained and compared from (a) symptom-oriented research interviews and rating scales (see M-AP(C)-16-1; -16-2); (b) individual research interviews oriented to formal or stylistic variables especially thought disorder; (c) psychotherapeutic work with schizophrenics and their families (see M-AP(C)-15-4); (d) interviews and records about pre-morbid history, kind of onset, and type of course of illness, especially thought disorder; (e) projective test scorings and evaluations (see M-AP(C)-14-2; -14-5), (f) scores from tests of sensory, perceptual, cognitive and psychophysiological variables (see M-AP(C)-21-52).

(2) To apply these various methods to patients from (a) a variety of cultures; (b) a variety of social class, educational and occupational backgrounds; (c) a variety of families, and to study how these social variables do and do not affect the individual features of the various forms of schizophrenic disorder.

Broadly speaking, this project serves to integrate data concerning schizophrenia obtained in a number of projects in the Branch and is especially concerned with developing improved, more comprehensive concepts and theories of schizophrenia. Especially relevant are M-AP(C)-14-2, 3, 5, 6; 16-1, 4; 21-2, 4.

Methods Employed: Work is continuing on the conceptualization and definition of a series of dimensions to which a variety of rating scales and test measures can be applied. These dimensions fall into five main clusters: (1) arousal, including alertness, energy level, and volitional and affective states; (2) selectivity with which attention is focused, irrelevant stimuli are excluded; (3) transactional sharing of foci of attention in which two or more persons look at the same events, ideas, or feeling states together, with differences along the dimensions of (a) active (doing) versus passive (undergoing) ways of relating to other persons and stimuli, and (b) variations in emotional closeness and distance; (4) organization of the boundaries and contents of the person's sense of self and sense of identity; and (5) patterns of variations in the above features through time in major or segmental "sets." The specific methods used are described in the various projects listed above which are brought together for purposes of conceptualization and theory formation in this project.

A major activity currently under way is to develop procedures for computerized analysis of the various kinds of data which have been, and will be, generated. Data have been obtained from over 1,000 subjects in various forms; much of this has now been coded into complex computerized data files.

Major Findings: This work both data analysis and the formulation and publication of concepts and theory, is actively in progress. It seems clear that the interview methods are, in fact, applicable to a variety of patients from different cultural and social class backgrounds and can be used reliably, but further testing and modifications will be carried out and reported in the future. It is also now clear that the various psychological test measures, both from projective tests (M-AP(C)-14-2, 5) and from perceptual, cognitive, and psychophysiological tests (M-AP(C)-21-2, 3), can be correlated in an illuminating way with the evaluations of clinical research.

Significance to Mental Health Research: The systematic evaluation of schizophrenic symptoms and processes is a fundamental necessity for further progress in this major area of psychiatry. This research program endeavors to bring together experimental and clinical approaches and to apply these to a variety of patients from different backgrounds. Too often in the past, sophisticated, experimental approaches have been related only to highly unsystematic and vague clinical evaluations, and only one or two variables of patients have been studied in most research programs on schizophrenics. For example, only chronic male patients of a particular social or educational background may be included in a given study. This piecemeal approach to the study of schizophrenics has led to many seeming contradictions in findings and in concepts which are difficult or impossible to resolve because the data obtained are not comparable from one study to the next. The present project

is conceived as a long-term program for developing assessment methods to a higher level of refinement and reliability than is presently available, and to increase the effort to apply and conceptualize these methods in relation to a broader spectrum of patients. These methods of data collection lend themselves to computerized data processing which permit the asking, and answering, of many research questions previously inaccessible to investigation.

Proposed Course of Project: Each aspect of the project will be continued and strengthened during the coming year with further collaboration of groups both within the Branch program and outside the Branch, as in the WHO International Pilot Study of Schizophrenia (see M-AP(C)-16-1). The current emphasis is on multivariate computerized analysis of the large amount of diverse data which have been assembled. The concepts and findings in this program are being assembled for publication in book form.

Publications:

(1) Wynne, L.C.: Communication Disorders and the Quest for Relatedness in Families of Schizophrenics. Amer. J. Psychoanalysis, 30: 100-114, 1970.

(2) Wynne, L.C.: Schizophrenics and Their Families. I. Research Re-Directions. Brit. J. Psychiatry, in press, 1971.

(3) Wynne, L.C.: Hearing a Different Drummer: Sources of Schizophrenia in the Family, Psychiatry, in press, 1971.

(4) Wynne, L.C.: On the Anguish, and Creative Passions, of Not Escaping Double Binds: A Reformulation. In press, Pergamon Press, 1971.

(5) Wynne, L.C.: Family Research on the Pathogenesis of Schizophrenia: Intermediate Variables in the Study of Families at High Risk. In Doucet, P. and Laurin, C. (Eds.): Problems of Psychosis, pp. 392-403, Amsterdam: Excerpta Medica, 1971.

Serial No. M-AP(C)-14-2
1. Adult Psychiatry Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Principles for Scoring Communication Defects and Deviances of Parents of Schizophrenics in Psychological Test Transactions.

Principal Investigators: Lyman C. Wynne, M.D., Ph.D. and Margaret T. Singer, Ph.D.

Other Investigators: Winfield Scott, Ph.D.; John Bartko, Biometry Branch, NIMH; Margaret Toohey.

Cooperating Units: Section on Twin and Sibling Studies, APB; Biometry Branch, NIMH; MRC Social Psychiatry Unit, Maudsley Hospital, London

Man Years:

Total:	2.2
Professional:	1.3
Other:	.9

Project Description:

Objectives: To apply previously developed theories about parental communication for evaluating protocols of psychological test transactions; to pinpoint selectively certain features of parental behavior which can be reliably and quite quickly scored from psychological tests, particularly the Rorschach, TAT, and Object Sorting tests; to evaluate inter-rater reliability using the scoring manuals; and to evaluate the effectiveness with which the scoring manuals can be used to differentiate parents of psychiatrically different offspring.

Methods Employed: In previous studies, Wynne and Singer have developed a series of principles for evaluating the forms in which persons engage and communicate in interpersonal relationships; parental styles of communicating in standardized situations are hypothetically linked to the occurrence and form of schizophrenic disorders in offspring. Wynne and Singer have hypothesized that communication problems of parents could affect the development of core ego functions which are, in fact, impaired in schizophrenics, including, most importantly, defects and deviances in the manner in which foci of attention are shared. These problems lead directly into a variety of other schziophrenic difficulties in such areas as the use of language, task orientation and interpersonal relations.

In evaluating these hypotheses, psychological test materials have been evaluated in ways quite different from their traditional use. The emphasis in the present approach is to regard these test protocols as "interpretive transactions" in which they are considered samples of communication obtained in a relatively standardized way in which the how (form) aspects are given more emphasis than the what (content) aspects of attending and communicating. Parental functioning in test transactions is studied with the viewpoint that the forms of this functioning (not the content) have certain counterparts in daily parental roles with the growing child, namely, showing the child (or, in the test situation of the individual Rorschach, the tester-listener) where to look, what it is he is to try to understand with the parent, and how he demonstrates his or her overall roles as a reasoning, communicating person. The tests were used to infer the effect the parent has on the other person transacting with him or her, and to analyze how the parent shares or fails to share a focus of attention with another person.

The scoring manuals have been designed for use with the Object Sorting test, individual Rorschach and TAT. It is necessary that records of subject-tester transactions be as nearly verbatim as possible. In the Rorschach scoring manual there are three main clusters of categories which are scored: closure problems, disruptive behavior, and peculiar perception and verbalization. Under these main headings there are 41 specific categories which can be used to score each response in the Rorschach. Similarly, somewhat different categories have been applied to TAT protocols and Object Sorting test protocols.

During the past year Rorschach data from a sample of 214 families (681 individuals) have been analyzed with this scoring procedure. One hundred and fifteen families were tested in Bethesda, 40 in London, and 59 in Houston. In this sample, a diagnostic diversity of patients of both sexes was included, as well as considerable social class and education variability. In the Bethesda samples, each parent and offspring was given a psychiatric diagnosis so that communication deviance scores and diagnosis could be compared for each individual and for parents compared to offspring. Subgroups of families have been parcelled out for special study. This approach has been facilitated by computerization of the data (see M-AP(C)-14-1) factor analyses, multiple regression analyses, and a stepwise multiple discriminant analysis of the data have been carried out in order to assess the significance of various demographic and clinical variables and the relative importance in various discriminations, of the particular categories in the scoring manual.

Major Findings: A high degree of inter-rater reliability was achieved in using the Rorschach scoring system. All protocols were scored entirely blindly, without any information about the diagnosis or relationships of any subject.

The central research hypothesis was decisively confirmed: in these intact families, the frequency of communication deviances of parents was significantly related to the severity of psychiatric illness in the offspring,

and when other variables are held constant statistically this relationship remains. A large number of new findings are emerging from these data analyses and are being prepared for publication.

Significance for Mental Health Research: This work has developed systematic, reliable scoring methods which are simple enough to be used by relatively untrained raters, but which make significant differentiations of parental behavior. The scoring methods have been directly derived from a comprehensive theory of psychological development within the family context which has been described in detail in a series of papers.

Proposed Course of Project: The concepts and findings in this study are being reported in a series of papers and in book form. The multivariate analyses of the data is in its final stages. The scoring procedure and manuals are being modified on the basis of the findings in the present study. The scoring procedure will then be applied to new samples of parents of different diagnostic, educational, social, and cultural backgrounds to discover what the limits of these procedures are as a predictive and screening device, applicable to the identification of "high-risk" versus "low-risk" subjects. Also, the procedure is being used with various special families such as adoptive families with and without a schizophrenic offspring. Such work will be valuable in elucidating the genetic versus the "learning" aspects of schizophrenic disorders. One study is currently in progress in which the Rorschach scoring manual is also being applied to a sample of parents of Japanese schizophrenics (see M-AP(C)-14-3).

Publications:

1. Wynne, Lyman C. and Singer, M. T., Schizophrenics and Their Families: II. Research Methods, Brit. J. of Psychiatry, 1971, in press.

2. Wynne, Lyman C. and Singer, M. T., Schizophrenics and Their Families: III. Recent Rorschach Communication Findings, Brit. J. Psychiatry, 1971, in press.

3. Wynne, L. C., Los esquizofrenicos y sus familias. Orientaciones y hallazgos de investigaciones recientes. In Sluzki, C. E., Berenstein, I., Bleichmar, H. H., and Allende, I. M. (eds.), Patologia y Terapeutica del Grupo Familiar, pp. 103-116, Buenos Aires: ACTA - Fondo para la Salud Mental, 1970.

Serial No. M-AP(C)-14-3
1. Adult Psychiatry Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Cross-Cultural Family Studies

Principal Investigators: Lyman C. Wynne, M.D., Ph.D. and Margaret T. Singer, Ph.D.

Other Investigators: Mieko Caudill; Dr. Kenji Sakamoto, Kyoto University Medical School, Kyoto, Japan; Dr. Y. Kasahara, Psychiatry Clinic, Kyoto University, Kyoto, Japan; Dr. S. Kuromaru, Kobe Medical School, Kobe, Japan; Dr. William Caudill, Laboratory of Socio-Environmental Studies.

Cooperating Units: Kyoto University Medical School, Kyoto, Japan; Sakamoto Psychiatric Hospital, Osaka, Japan; Psychiatry Clinic, Kyoto University, Kyoto, Japan; Kobe Medical School, Kobe, Japan; Section on Personality and Environment, Laboratory of Socio-Environmental Studies, NIMH.

Man Years:

Total:	1.2
Professional:	.4
Other:	.8

Project Description:

Objectives: To determine whether criteria for differentiating families of schizophrenics and other kinds of families apply cross-culturally and thus have generalized validity; to specify features of schizophrenics and their families which are and are not cross-culturally general; to study how variations in the sibling order of schizophrenics are related to cultural patterns of family life.

Methods Employed: Clinical data and psychological tests have been obtained from a sample of normal control families and families of schizophrenics in Japan, and earlier, in Lebanon.

This year emphasis was placed on examination of the Japanese data. Psychological test protocols have been received from families of 50 late adolescent and young adult Japanese psychiatric patients and from the parents of 20 childhood psychiatric patients and normal controls. These Japanese protocols are being translated and scored by Mrs. Mieko Caudill, a native Japanese, with the manual described in M-AP(C)-14-2, with the translated protocols also studied by Dr. Margaret T. Singer.

This year special attention has been given to a detailed examination of the problems of translating communication samples, as found in verbatim Rorschach records, from Japanese to English and vice versa. This study, conducted with investigators from both countries revealed much about the latent value assumptions and implicit communication processes in both cultures. Extensive discussions were also carried out on the problems of achieving diagnostic comparability on Japanese and American patients.

Major Findings: The project is still in progress. The preliminary findings indicate that the scoring manuals developed in the NIMH research can be used with these highly diverse psychological test samples obtained in Lebanon and Japan. Two papers on the special problems of conducting family therapy with large, extended families in a non-Western cultural setting (Lebanon) have been prepared.

Significance to Mental Health Research: The cross-cultural approach will very greatly strengthen the significance of the findings concerning the families of schizophrenics which have been obtained from American samples in the Adult Psychiatry Branch program. The patient-family links which have been studied in this research are concerned with forms of thinking and communicating, rather than the content of thinking, so that, theoretically, the methods of scoring should be applicable regardless of cultural background or other variables if there are characteristic forms in which families of schizophrenics relate and live with one another. Because of translating and other difficulties, there have been questions raised in many quarters whether psychological tests and interview materials can be meaningfully compared cross-culturally. The present study indicates that such work is practicable, if certain procedures and standards are used in translating and in obtaining the original protocols, but scrutiny of the translation problems is valuable in its own right because it facilitates understanding of cross-cultural differences.

Proposed Course of Project: Data collection in Japan by Drs. Sakamoto, Kasahara, and Kuromaru in Japan is almost complete. Interpretation of the findings, completion of publications on methodologic and substantive findings, and further planning of the collaborative work is in progress.

Honors and Awards:

(1) Wynne, L. C.: Polluted Values and Changing Families: Trends and Prospects. Presentation at the Conference on the Crisis of the Family in Modern Society, Family Institute of Philadelphia, September 24, 1970.

Publications:

(1) Wynne, L. C., Caudill, M., Kasahara, Y., Kuromaru, S., Higa, M., and Singer, M. T.: Problems in the Cross-cultural Study of Psychopathology: A Comparison of Japanese and American Disorders of Thinking and Communication. To be published, Lebra, W. (ed.): Mental Health Research in Asia and the Pacific, Honolulu: East-West Center Press.

Serial No. M-AP(C)-14-5
1. Adult Psychiatry Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Interpretation of Proverbs by Individuals and Families: Reconsideration of an Approach to Communication Disorder and Thought Disorder.

Principal Investigators: Lyman C. Wynne, M.D., Ph.D.; Margaret T. Singer, Ph.D.; L. David Levi, M.D.

Other Investigators: Cloe Sojit, Berkeley, California

Cooperating Units: Family Studies Section and Section on Clinical Psychology, APB

Man Years:

Total:	.3
Professional:	.2
Other:	.1

Project Description:

Objectives: To explore the usefulness of proverbs interpretation as a means of evaluating communication disorder and thought disorder with persons seen individually and in a family group. More specifically, to use and compare several methods for scoring proverbs interpretation with individuals; to develop a new scoring system for individual proverb interpretation based upon "transactional" principles previously applied to other psychological tests (see Project M-AP(C)-14-2); and to extend the method of proverb interpretation to conjoint family transactions without the participation of a tester.

Methods Employed: (1) As part of a larger psychological test program in the Section on Clinical Psychology, 164 individuals were given the task of interpreting a series of proverbs. These individuals came from families in which one or more members have been given a diagnosis of schizophrenia, borderline syndrome, neurosis or personality disorder, or psychiatrically normal. The proverb, "A rolling stone gathers no moss" has been regarded by several investigators as of special interest in proverbs interpretation because it has valid but opposite meanings and therefore presents a rather complex and perhaps "double-binding" task for the interpreter. Therefore, this proverb was selected for scoring by methods that have been previously advocated in the literature: a measure of verbal abstraction versus concreteness (Gorham), a measure of psychological differentiation maturity

(Becker), measures of concreteness and desymbolization (Benjamin), and a measure of task orientation (Richardson and Church).

Verbatim interpretations were blindly scored by two raters using each of these scoring methods. In addition, a new scoring manual was developed which was particularly applicable to this proverb; principles were adapted from scoring manuals previously developed for the Rorschach and Object Sorting Test. After the scoring was completed, reliability between raters was checked and a complex series of parametric and nonparametric statistical tests were applied to the data.

In an extension of a technique developed by Watzlawick and Sojit, parents in pairs were first asked to discuss the meaning of each of four proverbs and then to teach the meaning to their adolescent offspring. In order to evaluate the effects on the discussion of different degrees of familiarity and ambiguity, three proverbs, in addition to the "rolling stone" proverb, were used in the conjoint family testing situation. One of these was the familiar and quite unambiguous proverb: "All that glitters is not gold," and two were proverb-like inventions intended to elicit idiosyncratic meanings and connotations: "Quiet grows lilies" and "Women have shadows." The latter especially challenge subjects to form and select hierarchy of meanings - a special communication difficulty for schizophrenics and their families. In a pilot study conducted so far, three families of schizophrenic offspring with an "amorphous" form of communicating, three families with a schizophrenic offspring categorized as "fragmented" and three families without schizophrenic offspring but with an offspring having a history of delinquency were tested, first with the parents alone as a pair and then with the index offspring.

Major findings: The Gorham scoring procedure for individual proverb interpretation differentiated very poorly amongst the various groups of subjects. There appeared to be a tendency for more abstract interpretations to be found in subjects with higher education rather than with less serious psychopathology. Similarly, the Becker scoring procedure differentiated the subjects rather poorly. The Benjamin scoring procedure revealed that complete literalness was rarely found except in the schizophrenic patients and only in twenty-four per cent of them. A category recommended by Benjamin, "tinged with literalness" did not differentiate well. However, Benjamin's categories dealing with false desymbolization separated the groups better. A new 22-item scoring manual developed in the present project combined the Benjamin items, a Richardson and Church task orientation item, and an additional set of categories dealing with deviances of construction and style (form) of communication. In addition, an overall rating of comprehensibility was applied to each proverb interpretation, taking into account the total communication - including disqualifications and confusing introductions brought up by the subject, not simply the interpretation of the proverb itself.

Using both the comprehensibility rating and the total number of categories in the 22-item manual, a nonparametric statistical test revealed a highly significant differentiation between (a) parents of schizophrenics versus any of the other three groups of parents, (b) schizophrenic patients versus other psychiatric patients, and (c) nonsymptomatic siblings of schizophrenics versus nonsymptomatic offspring in the other groups. Within the families having a schizophrenic offspring, the parents showed a marginally significant tendency to have more deviance scores than their symptomatically ill offspring. The striking overall conclusion suggested by these results is that "communication disorders" are found in all of the members of the families of schizophrenics, not simply in the symptomatically ill members. Also, it was striking that the families of the schizophrenics could be definitely differentiated from the families of the quite similar borderline patients. These results still held up when the subgroups were controlled for education.

In the pilot study using proverbs interpretation as conjoint family procedure, the size of the sample test so far was too small for a statistical comparison, but has provided some interesting leads for further research. All of the families studied gave relatively clear and comprehensible meanings to the proverbs at the start of their discussion with one another, but in the families of the schizophrenics, there followed a series of disaffirmations or disqualifications which served to blur differences between the family members, ending up in a "pseudo-mutual" appearance of consensus not supported by agreement in the content of what was said. In contrast, the families of delinquent offspring engaged in direct and open conflict. Their inability to reach consensus became more and more clear as the discussion proceeded. Appeals to authority and interpersonal manipulation were used as a substitute for reaching a shared understanding about meaning.

Significance to Mental Health Research: "Thought disorder" and the broader concept of communication disorder have been widely regarded as core features of schizophrenia. Because the task of proverbs interpretation can be done easily and quickly, it is a potential technique for surveying large populations of subjects in a variety of studies in which it is important to locate persons at "high risk" for schizophrenic outcomes. The findings in this project definitely indicated that deviances are detectable even in the average of 40 words used in interpreting a single proverb; thus, even though an individual himself is not symptomatically ill, he may share an underlying feature of thinking or communication with symptomatically ill schizophrenics. This method of sampling communication may be usefully combined with other methods for picking up genetic or acquired vulnerability to schizophrenic disorder.

The leads from the pilot work with the conjoint proverbs technique suggest that an individual family member's communication pattern undergoes important transformations as a result of intrafamilial transactions. Because the verbal material with this method is relatively easily obtained without involving non-verbal measures or special experimental apparatus, it

may have advantages of practicality over other conjoint family research methods which are being tried out in the Branch program as well as in other centers.

Proposed Course of Project: The project is completed with the forthcoming publication.

Publication:

(1) Singer, Margaret T., Wynne, Lyman C., Levi, L. David, and Sojit, Cloe: Proverbs Interpretation Reconsidered: A Transactional Approach to Schizophrenics and Their Families. In Brunse, A. (Ed.), Language and Thought in Schizophrenia, 1968, (in press) 1971.

Serial No. M-AP(C)-14-6
1. Adult Psychiatry Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NSMA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Pilot Study in Records Codification

Previous Serial Number: NONE

Principal Investigator: James K. Dent, Ph.D.

Other Investigators: Lyman C. Wynne, M.D., Ph.D.; Margaret Toohey and Deborah Runkle

Cooperating Units: Section on Personality Development, Section on Clinical Psychology, Family Studies Section, Section on Twin and Sibling Studies.

Man Years:

Total:	0.3
Professional:	0.1
Others:	0.2

Project Description:

Objectives: The overall objective is to develop and evaluate the feasibility of a procedure for deriving standardized coded descriptions of psychiatric patients and members of their families from medical and research records. The system developed so far concentrates on symptomatic behaviors and social behaviors. The codification data obtained with this method is expected to be available for use in various research projects in the Adult Psychiatry Branch, but the method also is like to have more general application elsewhere.

Codification from records is of course limited by the quality and accuracy of the original observations. Since clinical descriptions are recorded for diagnostic and treatment purposes, omissions in an individual record may be an oversight or it may be that no attempt was made to ascertain whether a particular symptom was present for a variety of practical reasons. Codification is intended to permit investigators to group patients, according to their specific research purposes, on the basis of symptom patterns codified in a systematic and standardized way. Investigators can ascertain at a glance whether the quality of the record permits them to assign the individual within their classifications.

Methods Employed: It is assumed that codification will by done by assistants who generally do not have much training in mental health, (i.e. trained mental health professionals will not be available for this work). Corollaries of this requirement are:

(a) Codification should not require clinical judgment, as in concepts like "schizoid:, "autistic", and so forth.

(b) Codification should distinguish between reports of feelings and thoughts on the one hand and observable behaviors on the other.

(c) Reliability is enhanced very much if we emphasize "behavior".

(d) Codification should distinguish between a statement in the record, and a coder's inference from the record; coders should be discouraged from making certain kinds of inferences.

(e) If possible, codification should specify at what time the symptoms were present; at admission, preepisodic, and so forth.

Major Findings: The categories for symptomatic behaviors and social behaviors were applied to six additional families with results very much as reported last year.

Significance to Mental Health Research: Objective description of severe disorders is plagued by many difficulties. The patient is frequently an inadequate respondent because of his defensiveness and because he does not remember events or his own behavior during states of confusion. Any particular observer has only a sample of behavior to report and those observers with the largest preadmission sample (the family) are frequently the least objective. Important information about the patient or his sibs (e.g., lawless behavior) may be concealed and come to light only after months of rapport-building in therapy.

There is therefore no single source for a complete objective description of persons with severe disorders. The best description is likely to be one which uses all information available from a variety of sources.

The medical records of the Clinical Center and the research records of the various projects in the Adult Psychiatry Branch are a particularly rich resource for the description of mental disorders, because of extensive descriptions from many family members over long periods of time. In fact it is doubtful that such a wide variety of materials is available anywhere else.

This is not to say that the records are ideal for the systematic description of disorders and their course. As noted above, gradual changes tend not to be reported. WHO type interviews (see M-MP(C)-16-1) are useful in this regard

but it is probable that a simplified system of description for use over time also is needed. Nevertheless, systematic summarization of our records serves a useful purpose for a number of present and future research projects.

Proposed Course: This project was suspended in December for want of suitable help. At that time we had progressed to the point where measures of inter-rater agreement were needed. It is likely that an intelligent undergraduate of suitable temperament can be trained to do this coding in a week or two, but because of issues of confidentiality, this work cannot be performed by volunteers. There being no available help to take the next step, the project was suspended. The forms and instructions are available, should anyone wish to pursue these purposes at a later date.

Honors and Awards: NONE

Publications: NONE

Serial No. M-AP(C)-14-7
1. Adult Psychiatry Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Pilot Study in Securing School Records of Patients and Their Siblings.

Previous Serial Number: SAME

Principal Investigator: James K. Dent, Ph.D.

Cooperating Units: Montgomery County Board of Education

Man Years:

Total:	0.05
Professional:	0.05
Other:	0.00

Project Description:

Objectives: Our purpose is to ascertain whether we can economically secure school records for patients and their siblings.

Methods Employed: The tasks are: (1) to secure a release or request signed by a responsible party, usually a parent, and (2) to secure the record from the appropriate school system.

Major Findings: As indicated last year, we have managed to secure release forms for two-thirds of a sample of discharged patients. In a few cases, the request of such a release form from the parents of a discharged patient has been resented. It is clear that the most effective way to get school records is to secure release forms for the appropriate school systems at the time of admission.

As for the cooperation of school systems they are accustomed to providing this kind of information. However, records are decentralized and for this reason considerable follow-up is necessary. Based on our experience with Montgomery County this process is not excessively time-consuming.

Even within a single system there appears to be considerable variation in record content. However, almost all records contain the following: grades, attendance, achievement test scores, a measure of verbal I.Q.

Significance for Mental Health Research: School records provide objective measures of the premorbid functioning of the patient, and parallel descriptions for his siblings. Among their uses are the following:

1. They nearly always contain at least one IQ test. This provides a premorbid measure for the index. For some patients who are not testable for one reason or another, it may provide the only available IQ measure.

2. They always report attendance and grades. Sudden deterioration in performance is not necessarily indicative of rapid onset of symptoms, but gradual deterioration tends to rule out rapid onset. In the development of standardized histories, the onset has posed particularly difficult problems in measurement.

3. Behavior problems are frequently noted, and sometimes a complete psychological work-up is available.

Proposed Course: No further efforts to secure records will be undertaken at this time. The records we have will be given further analysis and results will be reported in a summary paper. It is expected that this project will be completed during the 70-71 fiscal year.

Honors and Awards: NONE

Publications: NONE

Serial No. M-AP(C)-15-2
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: A Study of the Separation Process in Adolescents and Their Families

Previous Serial Number: SAME

Principal Investigator: Helm Stierlin, M.D., Ph.D.

Other Investigators: Joseph H. Herzberg, M.D., Stanley I. Hirsch, Kent Ravenscroft, Jr., M.D., Robert J. Savard, Ph.D., Miss Elizabeth Sherwood, John S. Strauss, M.D., David Wember, M.D., and Lyman C. Wynne, M.D., Ph.D.

Cooperating Units: Pupil Personnel Section, Montgomery County Schools (Maryland); Section on Clinical Psychology; Section on Perceptual and Cognitive Studies; Section on Psychiatric Assessment (Adult Psychiatry Branch, NIMH).

Man Hours:

Total:	7.3
Professional:	5.5
Others:	1.8

Project Description:

Objectives:

The basic objectives of this study have remained the same as stated in the report of last year: To investigate, at the clinical and research levels, the individual and family factors which may further or jeopardize the separation process throughout adolescence. By tapping a large available reservoir of students with school problems, the study makes use of an adolescent high risk population who, over the next five years, will or will not develop either in a psychotic or sociopathic direction. Understanding and possibly differentiating the separation course of these two patient groups is the main goal. This includes a grasp of these patients' family and peer relations as they unfold in time. The project builds on many of the findings which Drs. Lyman C. Wynne and Margaret T. Singer and their associates have reported during the last decade. It addresses itself now to those experiential factors which may allow certain high risk adolescents to steer clear of serious psychopathology while

causing others, of seemingly equal or even lower risk, to succumb to such psychopathology.

Within the framework of this broad objective, the study tries further to throw light on several specific related issues. These are:

(a) Parental perceptions and expectations which specifically bear on their children's separation, e.g. their ability and willingness to seek partners outside the family or to take on responsible jobs. We have become increasingly impressed with the importance of such perceptions as factors which either inhibit or promote their children's moves toward autonomy.

(b) The individual and family dynamics of runaway adolescents. Twenty-four out of 37 index adolescents seen in this project had run away from home at least one full day and night, before they had turned 17 (some of them have run away frequently, getting as far away as Florida, California and Canada). The project offered a unique chance to study in depth this group of runaways.

(c) In addition to these more recent research foci, we have continued to remain interested in three issues mentioned in last year's report: (1) The often strikingly divergent developmental course of siblings who appear close in age and who, at first sight, appear exposed to similar family influences; (2) the sequelae of an early precocious and over-stimulated development, and (3) the potential problems and limits inherent in various treatment approaches - but mainly individual and family therapy - as used during the crucial juncture in an adolescent's life and separation process.

Methods Employed:

Adolescents of age 15 and 16 who attend public schools in Montgomery County (Maryland) continue to supply the bulk of our patient material, in addition to those referred to us by private psychiatrists and various social and psychiatric agencies. The various referral sources send us adolescents who demonstrate school problems and whose families appear willing to engage in family therapy. It is assumed that these students represent a high risk population both in the direction of schizophrenia and in the direction of sociopathic development. Broken and unbroken families are accepted. At the initial screening appointment, the family is seen as a group for 50 minutes and then the couple and designated patient are seen each for one-half hour. If the family qualifies and is willing to participate in the treatment and research project, the patient is admitted to Unit 3-West where he receives individual psychotherapy, usually three times a week. The family is seen in once- or twice-weekly family therapy sessions. Couple therapy once a week is mandatory. Individual psychotherapy for family members is offered when necessary and feasible. On the ward, the intensive therapy of the individual adolescent is supplemented by an intensive milieu program. No time limits are set to the individual or family treatments.

After the first screening interview the available historical, social and dynamic data about the family are summarized and a fairly detailed prediction is made about the index patient. This prediction includes ten items such as employment in five years, psychiatric contacts and diagnoses, suicidal tendencies, delinquent tendencies, etc. The ensuing family and individual therapy is then used to obtain a more comprehensive picture of the family dymamics as they fear on the adolescent's separation problem and further development. The following areas are carefully observed and assessed:

(1) The prevailing parental perceptions and expectations, particularly insofar as these bear on the adolescent's separation.

(2) All data pertaining to runaway episodes of adolescents, e.g. overt or covert parental encouragement, the context of the running away episode, antecedents, peer contacts, etc.

(3) The communication patterns within the family. We try to establish how much each family is able to share a common focus of attention and how much their communications in one way or another are bound to sabotage a pooling of resources.

(4) The nature of the family's alignments, their relative shifts and inconsistencies, their strengths, and their overt- or covertness.

(5) Family boundaries. We try to assess how the family is integrated within the community and how much it might put obstacles in the way of the adolescent's associating with peers, teachers and other figures outside the family.

(6) Patterns of psychological exploitation: The various ways in which a child (more or less covertly) is recruited to serve his parents in ways which interfere with his own growth and separation.

(7) We try to be alert to all data, implicit and explicit, which throw light on the parents' own separation problems when they were adolescents themselves.

(8) Through an actively and empathically conducted family therapy, we try to get an indication of how much the family might be capable of changing its patterns and facilitate the adolescent's separation. Also, by focusing on the evolving transferences, we try to get further clues about the parents' own separation problems.

On the basis of these assessments, which are supplemented by an individual interview with each family member, we make, at the end of the treatment period, second step predictions about the adolescent's prospective life style at the age of 21. These predictions cover the same items as those made immediately after the screening session, but they are now more amplified. Also, we supplement them by a narrative kind of prediction in which we deal with the question of how much the index

will become restricted or nonrestricted, active or more passive. In cases where there are two siblings closely related in age, the two of them will be covered by predictions. It is expected that the later confirmation, partial confirmation, or refutation of our predictions will deepen our insights and sharpen our hypotheses about the adolescent separation process. The comparison between the first step and second step predictions, as outlined above, appears as a useful means of alerting us to possible sources of predictive error at this early stage of the research project.

While the principal clinical investigator tries to make five-year predictions based on the assessment of presumably crucial and lasting family features, as mentioned above, additionally obtained Rorschach tests, TAT, cognitive and perceptual style procedures of all family members, as well as the audio and video tapes, provide material for independent evaluations and predictions to be made either now or at later stages of the project. The availability of these test procedures makes it further possible to utilize these families for other ongoing research projects of the Adult Psychiatry Branch, as described elsewhere.

Further, a standardized diagnostic inventory is made in accord with guidelines developed by Drs. John Strauss and Will Carpenter on all newly admitted index patients. This should provide us with a further means to check out (subjectively tinged) dynamic family data against other independently obtained and more standardized data.

Altogether 37 index patients and their families have so far been included in the program. With one exception, only inpatients have been accepted during the past year. As in previous years, a number of families were seen in screening sessions only. These families, too, were made subject to predictions so that they can be followed-up and can serve as untreated controls to the treated index patients and their families.

In line with our growing interest in the problems of runaways, we have tried to gain additional information about this adolescent group from various sources. The available literature on runaways was thoroughly studied. Dr. Herzberg continued to serve as a consultant to the Runaway House in the District of Columbia where he could observe a somewhat different runaway group than the one found at NIMH. Also, Dr. Stierlin, in a more informal way, tried to make contacts with various teenage runaways whom he met in either a professional or non-professional context. Dr. Stierlin's group therapy with adolescent drug addicts at The Johns Hopkins Hospital in Baltimore had to be discontinued for practical reasons.

Chiefly due to the lack of manpower, no systematic follow-up studies of formerly treated patients could be conducted this year. However, information relevant to runaway episodes of the index patients and their siblings was obtained through telephone conversations with a large number of family members.

Major Findings:

Although this is a longitudinal study whose major findings cannot be expected before one or two more years have elapsed, the following interesting findings can be noted.

(1) Two major separation patterns in adolescence, called centripetal and centrifugal, have been delineated. In the centripetal pattern family and individual factors combine to bring about an "inward movement" of the adolescent. This adolescent delays his separation; he tends to emerge himself in a fantasy world while remaining entangled with his parents. Typically, these adolescents are schizophrenic or schizoid individuals. In the centrifugal pattern, individual and family factors combine to promote a precipitous outward movement of the adolescent. Typically, these adolescents become early separators who try to substitute peer life for family life. A large number of them have sociopathic characteristics. Various implications for the adolescents' cause of these two separation courses could be outlined. Also, certain intermediate patterns between the above two extreme patterns can be delineated.

(2) Parental perceptions and expectations which either induce or block their adolescent separation could be more clearly described. In particular, their overtness and covertness, their mystifying nature, and their implications for family therapy could be established.

(3) We have further differentiated various exploitative transactional modes of parents which we have called the modes of binding, delegating, and expelling. All these parental modes contribute to a distorted separation of adolescent children. They operate via perceptions and expectations but also imply more basic relational ways and styles.

(4) Five types of teenage runaways have been delineated. These types seem to reflect different family constellations and appear to have different implications for therapy. Particularly interesting appeared a group of lonely schizoid runaways who did not tend to have the peer contacts which the other runaways had, and a group of abortive runaways who would run away for very short periods of time only, thereby reflecting their ambivalence about wanting to separate and, at the same time, feeling bound to their families. These five types of runaways have, in turn, helped us to delineate the transactional parental modes described under (3) above. Various papers describing the above findings are being prepared or are being published.

(5) The family dynamics and separation patterns which affect potential schizophrenics came more into focus.

Significance to Mental Health Research:

This study builds on findings about the structures, communication patterns, and boundaries of families with disturbed offspring which have been made at the Adult Psychiatry Branch during the past decade. With the focus on longitudinal development and the separation process in adolescence, this study tries to assess the significance of various - mainly experiential - factors in the actual outbreak of schizophrenia and other disturbances during late adolescence, a period which is known to be fateful in an individual's personality development and which yields a high percentage of first schizophrenic breaks. The new focus on runaways appears commensurate with the increasing social importance of this patient group.

In the present study, family therapy is used as a diagnostic instrument. At the same time, it is tried out as a possibly efficient and most economic tool in the prevention of the major disasters of late adolescence.

Proposed Course of Project:

A major effort will be made to make interim follow-up interviews on the approximately 40 families who so far have passed through this project. At the same time we will continue to admit new families to the extent that our ward capacity and manpower resources permit. We hope to see more lower-class families since these are badly under-represented in our sample. Also, more emphasis will be placed on couple therapy and milieu therapy as important treatment modalities. We plan to pay more attention to the peer group so as to obtain a better understanding of the problems resulting from a precocious substitution of peer ties for family ties. No major changes are planned in the methodology of this project as these have been outlined in previous reports.

Honors and Awards: NONE

Publications:

Stierlin, H.: Familientherapie mit Adoleszenten im Lichte des Trennungsprozesses. Psyche XXIV: 756-767, 1970. (The English version of this paper will appear in Canada's Mental Health, 1971.)

Stierlin, H., Levi, L. David, and Savard, Robert J.: Centrifugal versus centripetal separation in adolescence: Two patterns and some of their implications. Accepted for publication in Annals of the American Society for Adolescent Psychiatry.

Serial No. M-AP(C)-15-3
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-NSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Evaluation of Family Dynamics with Conjoint Family Art Procedures

Previous Serial Number: SAME

Principal Investigator: Hanna Yaxa Kwiatkowska

Other Investigators: Marilee Shapiro

Cooperating Units: Family Studies Section, Personality Development Section, Twin and Sibling Section

Man Years:

Total:	0.6
Professional:	0.3
Others:	0.3

Project Description:

Objectives: The purpose of the project is: (1) To evaluate families through a technique in which art media are used as a mode of communication and self-expression in order to compare (a) different families in which one or more of the offspring is afflicted with one of a variety of mental illnesses (schizophrenic, psychoneurotic, or delinquent) as well as normal families, and (b) different members within a family; (2) to evaluate through the same technique changes occurring in the course of family psychotherapy by repeating these procedures in periodic follow-ups during the treatment and after discharge.

Methods Employed: (1) All members of a family are seen jointly in art evaluation sessions. The family is introduced to easy art media with no emphasis on artistic achievement. The structure of the session combines spontaneous self-expression with standardized procedures: (a) free picture; (b) family portraits; (c) abstract family portraits; (d) individual pictures started with the help of a scribble. These procedures originated from the most significant material appearing repeatedly through the years in patients' and families' spontaneous art work in the course of family art therapy and are devised for the comparison of different families. The sessions are conducted by the art therapist with a cooperating investigator-psychiatrist, psychologist or social worker--as participant observer. All the sessions

are tape recorded, most of them video taped for a better study of family interaction. Abstracts of all the sessions, describing the families' transactions, their comments and discussions of their pictures as well as special observations of the investigators, are dictated upon completion of the session; the art productions and tapes of the sessions are studied for more accurate analysis. Each family is seen in a single evaluation session within the first two weeks of admission. Long term patients and their families are seen in a second family art evaluation after a minimum of six months of conjoint family therapy or at termination of treatment.

The families admitted to the Family Studies and Personality Development Sections have continued to participate in family art evaluations. As in previous years the art therapist had as minimal as possible contact with the patient or family prior to the evaluation in order not to be biased by information from other sources.

The methods of systematic analysis of material obtained from family art evaluations at the National Institute of Mental Health and the Institute of Psychology of the Catholic University in Rio de Janeiro, Brazil are described in projects No. M-AP(C)-15-9 and M-AP(C)-15-8.

Major Findings: In the period from May 1970 to April 1971 all but one family admitted were seen in a family art evaluation. Similarly to last year the investigated patient population in the period from July 1, 1970 consisted in great majority of adolescents with behavioral problems such as delinquency and drug usage. The investigation of phenomena specific to families of patients with these types of mental disorders, which were observed last year has been continued. Special attention has been given to the study of the impact of the family transactions on the youngest member participating in the family art evaluation sessions. This sample consists of children between the ages of 8 and 14. They frequently displayed in verbal family therapy a detached attitude and uninvolvement in the problems of the family. Their pictures consistently revealed the opposite, ranging from depression and anxiety to signs of underlying serious psychopathology. These findings are valuable additions to the planning of preventive treatment.

As in preceding years the family art evaluation, basically a research procedure has also presented clinical advantages. The pictures displayed at clinical conferences illustrate the family members' problems, their transactional style and their perception of each other. The clinicians can visualize and focus on specific issues represented in the concrete and durable form of the graphic projections. These issues can also be further worked on in family or individual therapy.

Significance to Mental Health Research: The development of this new technique continues to give additional dynamic understanding of family relations to projects of the Adult Psychiatry Branch of NIMH. The hypotheses based on the empirical findings obtained through family art evaluations are being scientifically investigated by systematic computer analysis of the material and

described as a separate project (M-MP(C)-15-8).

The researchers' and clinicians' interest in this technique has noticeably increased this year in the United States and abroad.

Seminars on family art techniques, reprints of papers and consultations are constantly requested from the Art Therapy Unit.

Proposed Course: It is proposed (1) To continue to evaluate through conjoint family art procedures the psychodynamics of families of patients investigated in the Adult Psychiatry Branch of the National Institute of Mental Health. (2) To further assess the therapeutic change as well as the permanence of characteristic traits in the family by repeating the family art evaluations. (3) To further investigate the impact of the family problems on the youngest member of the family participating in the family art evaluation sessions; (4) To perfect and revise video tapes of family art evaluations for educational purposes in view of increasing requests from different training centers and universities. The interest in training in family art techniques has extended to other disciplines, e.g., a seminar was requested by the Catholic University in Washington, D.C. for graduate social work students, for the Mental Health Associate Program at Montgomery College in Montgomery County, for the Nursing Staff and for the Patients Recreation Section of the National Institutes of Health. Seminars and workshops have been held for numerous other groups such as: The American Art Therapy Association, the Menninger Foundation, the George Washington University Hospital, and the Washington School of Psychiatry.

Honors and Awards: NONE

Publications: **Mosher, Loren R. and Kwiatkowska, Hanna Y. Family Art Evaluation: Use in Families with Schizophrenic Twins. Accepted for publication in Journal of Nervous and Mental Diseases.**

Serial No. M-AP(C)-15-5
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Family Art Therapy

Previous Serial Number: SAME

Principal Investigator: Hanna Yaxa Kwiatkowska

Other Investigators: NONE

Cooperating Units: NONE

Man Years:

Total:	x	
Professional:	x	(inactive)
Other:	x	

Project Description:

Objectives: (a) To further investigate the pilot study where family art therapy is used as the sole therapy with families of adolescent schizophrenics; (b) To use this approach with families of different socio-economic backgrounds; (c) To further collect data on the blind reconstruction and evaluation of the therapeutic course of a case treated by long term family art therapy; (d) To revise for final publication, now enlarged to the form of a monograph, the paper "The Use of Drawing and Painting as a Primary Medium for Communication in the Family Therapy of Schizophrenia."

Methods Employed: All members of a nuclear family are seen jointly in family art psychotherapy by the art therapist and the collaborating psychiatrist. Art media are offered to the family as a means of communication and self-expression; artistic or aesthetic considerations are not emphasized. In some of the sessions (at the beginning of treatment and repeated every six months) art evaluation procedures are used. These procedures combine free expression with standardized tasks and their purpose is to periodically gauge the course of therapy. Otherwise the family is largely left to structure the session; they are encouraged to draw or paint whatever comes to mind. It is advisable as a general principle to use drawing and painting periodically, not constantly--graphic expression can be used by the family defensively to cut off discussion of painful or difficult issues. Experience showed that with certain types of families the active participation by the therapists in the drawing was helpful and this change is introduced when

needed. All sessions are tape recorded; abstracts describing the family's interaction and the analysis of the pictorial and verbal material, as well as the therapists' subjective reactions, are dictated by both therapists. In the course of therapy at least one session is video taped.

Major Findings: No family was investigated this year:

(1) There was no family available for the use of this technique,

(2) Current work on family art evaluations (Project M-AP(C)-15-3) and on the systematic analysis of material obtained from the art evaluations (Projects M-AP(C)-15-9, 15-10 and 15-8) occupies all the available time.

Proposed Course: To continue, when time is available, in collaboration with staff psychiatrists, using art therapy as the only therapeutic procedure with families of schizophrenics and psychoneurotics. To continue when indicated, family art therapy as an adjunct to psychotherapy. To complete and present for publication the monograph "The Use of Drawing and Painting as a Primary Mode of Communication in the Family Therapy of Schizophrenia." The main focus of the work is at present on the third part of the monograph: "Family Art Comparison Study", a "blind" analysis of eminent psychiatrists and analysts of pictorial material obtained from long term family art psychotherapy and chronologically arranged. This part of the study has been prepared for presentation at the American Psychiatric Association meetings in Washington, D.C., in May 1971.

Honors and Awards: NONE

Publications: NONE

Serial No. M-AP(C)-15-6
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Conceptualization of Lasting Dyadic Relationships

Previous Serial Number: SAME

Principal Investigator: Helm Stierlin, M.D., Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.3
Professional:	.2
Others:	.1

Project Description:

Objectives:

This project seeks to contribute to the theoretical base for the comparative analysis of a wide variety of human relationships. It grew out of conceptualizations which the investigator developed before he joined the Adult Psychiatry Branch five years ago and which were published in book form (Conflict and Reconciliation. New York: Doubleday-Anchor, 1969; New York: Science House, 1969). The focus continues to be on the ongoing transaction between two persons who are considered as subjects - that is, as centers of an individual orientation toward the self, the world, and the other - and who are changed while the relationship unfolds. The phenomenology and dynamics of psychological exploitation appear here particularly significant. The implications of a dyadic model for the better understanding of family and group relationships are being explored. Also, creativity as a response to a binding and conflictual interpersonal field has been made a special focus of study.

Methods Employed:

Study, critical evaluation and integration of a wide range of ideas and findings reported in the literature on human relationships. At the same time, the project relies increasingly on the clinical experiences and observations provided through the clinical services of the Adult Psychiatry Branch and particularly the ongoing family therapies. Increasingly, the

issues raised and described in Project M-AP(C)-15-2 have influenced the here-described conceptual efforts.

Major Findings:

(1) The concept of psychological exploitation is being developed and clarified. From this conceptual angle it becomes increasingly meaningful to differentiate, among many other things, between what might be called exploitative and generative transactional modes, the former being defensive and restrictive and the latter growth- and autonomy-inducing. The investigator is still in the process of putting these thoughts into book form. This is then expected to serve the conceptual base for an understanding of those separation vicissitudes which are the concern of Project M-AP(C)-15-2 and which have been described there.

(2) Various more or less related subjects, mentioned already in the previous report, have been further worked on. These include a paper on "The Functions of Inner Objects," and one on the German poet Friedrich Holderlin (1770-1843) who became clinically schizophrenic in his mid-30s.

Significance to Mental Health Research:

This conceptual work is relevant to the understanding of schizophrenia as a transactional thought disorder. Beyond that, it seeks to illuminate various mental disorders as being linked to special types of human relationships. The complexities of human relationships, it appears, have far outdistanced the conceptualizations so far at our disposal. This project tries to reduce the conceptual lag in this area. The concept of psychological exploitation seems relevant to many pressing social issues.

Proposed Course of Project:

A number of theoretical papers are being prepared or are under revision. Therein the investigator expands on the issues and ideas mentioned earlier.

Honors and Awards: None

Publications:

Stierlin, H.: The functions of 'inner objects.' Internat. J. Psycho-Anal. 51: 321-329, 1970.

Stierlin, H.: Book Review of E. Weigert's The Courage to Love: Selected Papers. Psychiatry 33: 540-542, 1970.

Serial No. M-AP(C)-15-7
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Siblings of Schizophrenics; Personality Patterns in Family Members

Previous Serial Number: SAME

Principal Investigators: Juliana Day Franz, M.D.; Carol Hoover, MSSW.

Other Investigators: James K. Dent, Ph.D.; Hanna Y. Kwiatkowska

Cooperating Units: Unit on Art Therapy (Family Studies Section); Division of Computer Research and Technology (Biometry Branch, NIMH)

Man Years:

Total:	0.8
Professional:	0.7
Others:	0.1

Project Description:

Objectives: To develop an understanding of the personalities of the individual members of the family of the schizophrenic, not only of the immediate family of the patient, but also the connecting families in other generations. An assessment of character, thought disorder, ego strength and the potentiality for establishing relationships is made as well as a description of constitutional differences, and early parental assignment of role and identity. Mothers are interviewed in an attempt to have them define the difference in their maternal experience with each of their offspring.

Methods Employed: Included in this study were all families belonging to the Short-Term Studies of Families [M-AP(C)-15-4], families engaged in the now-terminated project, Family Dynamics and Conjoint Family Therapy [M-AP(C)-15-1], as well as some families seen in other projects such as the Study of the Separation Process in Adolescents and Their Families [M-AP(C)-15-2]. The parents, as a couple, and all other members of the nuclear family as well as other available members of the extended family were interviewed individually. The mothers of the index patients filled out forms giving information on pregnancy, birth and developmental landmarks for each offspring and in a semi-structured interview were asked to describe the day of delivery for each of their children.

Major Findings:

Fifty-seven siblings were less entangled in the family emotional life than thirty schizophrenic patients in the same families. Level of illness in siblings was associated with the degree of family entanglement.

It appears, however, that the percentage of these siblings at various levels of illness may not differ from proportions to be found among young persons in the general population.

No correlation could be found between the patient's rank order of health and that of siblings in the same family.

The siblings did not fit a single pattern in personality, but fell into several clusters which were characterized by different survival styles within the family of origin.

Significance to Mental Health Research:

This study attempted to describe the range of personality patterns in the family of the schizophrenic. It attempted to define how it comes about that there is such a spectrum of influence upon the developing children.

This work interrelated and was influenced by many other programs of the Institute which examine the heredity and environmental factors in schizophrenic illness.

Proposed Course of Project:

This interview study, focusing upon the levels of illness, social functioning, and family entanglement of siblings in the families of schizophrenics, has now been completed. Results were presented to a meeting of the Adult Psychiatry Branch in September 1970, and the material has been accepted for publication.

Honors and Awards: None

Publications:

Hoover, C.: Prolonged schizophrenia and the will. Accepted for publication in the Journal of Humanistic Psychology.

Hoover, C. and Franz, J. D.: Siblings in the families of schizophrenics. Accepted for publication in Archives of General Psychiatry.

Serial No. M-AP(C)-15-8
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Systematic Analysis of Family Art Evaluations

Previous Serial Number: SAME

Principal Investigators: James K. Dent, Ph.D. and Hanna Yaxa Kwiatkowska

Other Investigators: Lyman C. Wynne, M.D., Ph.D, Margaret T. Singer, Ph.D.

Cooperating Units: Section on Personality Development, Section on Twin and Sibling Studies, Section on Clinical Psychology, Division of Computer Research and Technology.

Man Years:

Total:	1.00
Professional:	0.45
Other:	0.55

Project Description:

Objectives: The overall objective is to explore systematically the materials available from the Family Art Evaluations which have been introduced by Mrs. Hanna Kwiatkowska and conducted for several years. Such an analysis is aimed at improving diagnostic procedures and increasing our understanding of the social psychological dynamics of psychopathology. In presenting the specific objectives, the longer range of objects are listed first; the immediate objectives are listed last.

A. Family Dynamics and Psychopathology.

1. To define the connection and temporal sequence between individual psychopathology as expressed in the family members' pictures and the family transactions in the structured setting of the Family Art Evaluations.

2. To differentiate, through the characteristics of their art productions, families in which the index is diagnosed as process schizophrenic, reactive schizophrenic, psychoneurotic, and so forth.

3. To distinguish role positions in the family (father, mother, sibling, etc.), as revealed by their pictures (such as family portraits) and transactions.

B. Diagnostics (A Manual for the use of the Family Art Evaluations).

1. To specify the relation of the diagnosis of the index to the characteristics of his own art productions and those of his family.

2. To determine which characteristics of the art productions appear to represent transient symptoms and which represent more enduring personality characteristics.

C. Measurement Objectives.

1. To develop objective rating systems for pictures and family transactions in the Family Art Evaluation method.

2. To determine the interrater agreement and the internal consistency of the scales used.

3. To construct by combining scales, variables having stronger metric power.

4. To analyze the significance of variables like artistic talent and intelligence which may confound the relation between diagnostic variables and characteristics of the art productions. It is important to separate the evidence of psychopathology in a picture from the influence of intelligence or artistic talent.

Methods Employed: Our methods were described in detail last year. In summary, the pictures are blinded, randomized, and rated; One picture in four is check rated for studies of interrater agreement. A variety of statistical techniques are being used, depending upon specific objectives.

"Blind" ratings of pictures represent an independent measure of the mental status of an individual at a particular point in time. It is our plan to correlate these ratings with other data. Correlation with diagnosis and family characteristics such as socio-economic status will be greatly facilitated because some of these data have already been compiled in connection with the research done by Dr. Lyman C. Wynne.

As a measure of mental status at a particular point in time, these ratings can be related to the events immediately **preceding** or following the moment when the picture was drawn. Such events might be family transactions occurring during the session. The combination of the two types of analysis, the correlation and the temporal, should enhance our understanding of the role of family dynamics in mental disorder.

Major Findings: The past year was spent chiefly in preparing for analysis (1) the ratings of the 1,525 pictures, and (2) diagnostic information about the patients.

Studies of interrater agreement and of rater bias suggest that the descriptive dimensions of the rating system will be of more value to us than the subjective ones. (In studies of drawings of mental patients, there is a predominance of subjective ratings.) One sub-study of rater bias was concerned with the raters' preferences for the pictures and the results of this study were presented at the IV International Colloquim, International Association of Empirical Aesthetics, Glasgow, Scotland, 17-19 August 1970.

The findings of this study may be summarized, as follows:

1. Even when the pictures vary greatly in aesthetic quality, individuals do not agree about which pictures they like. There is a measure of agreement between raters, but there is considerable disagreement as well. The disagreement seems to arise because individuals use different criteria for evaluation.

2. Some persons viewing a picture evaluate its pleasing and displeasing qualities as separate and independent items. They may see in the same picture a lot of pleasing qualities and a lot of displeasing qualities. Other viewers tend to form an overall impression which is positive or negative and to project the feelings from one dimension to another. Thus, some individuals see "ugliness" as the opposite of "beauty" while others do not.

3. Tastes are quite specific and can be measured. One individual may be influenced most by color, while another concentrates on the comprehensibility of the content. A rater's dislike of indecisiveness may be strong enough to override the effects of other characteristics.

4. There appear to be only a few characteristics of pictures which are generally appreciated by most individuals (coloring in and comprehensibility), and a few which are generally disliked (destructiveness and fragmentation). It will be interesting to see whether other studies corroborate these apparently general aesthetic preferences.

5. Personality measures for the 10 raters reveal some meaningful relations between certain groups of personality items and certain tastes in pictures. These relations might be stated tentatively, as follows: Persons who value comprehensibility in pictures place a high value on individual intellectual achievement and on emotional control. Persons who dislike fragmentation seem to dislike the unfinished, the imperfect, and the unexpected. They also tend to dislike ambivalent feelings. Persons who like lots of different colors enjoy a realistic and constructive freedom of expression. For those who like to see shapes colored in there may be a need for order and control.

Significance to Mental Health Research: Since the art production is an independent, enduring representation of the mental status of an individual (or family) at a moment in time and in a structured family setting, it is a valuable datum both for enhancing our diagnostic methods and for investigating family dynamics in relation to mental disorder.

The usefulness of "drawing tests" for individual diagnosis is widely recognized. Considerable research has been done on the Draw-A-Person test. More recently there have been efforts to use other types of art productions. Although the literature is full of ideas about how to diagnose mental illness from pictures, most of the research has been concerned with a much simpler and less useful task, viz.: To predict whether a person is mentally ill. Only a few systematic studies (e.g., that of Dr. Robert Kaye) have been concerned with trying to specify what aspects of a picture are predictive of what kinds of mental disorder, and there have been no statistical studies of family d namics as seen through the art productions of the whole family.

On the side of family dynamics, there is a rich body of research findings. Many of the concepts in this literature are used in the present study. Moreover, the material is being coded for the computer in the same format as for other studies in the Adult Psychiatry Branch, and this will greatly facilitate the comparison and integration of findings.

Proposed Course: During the remainder of the present fiscal year we will complete the accumulation of data regarding psychopathology in these 72 patients, and we will begin the final analysis of the joint relations of picture characteristics, intelligence, artistic talents, and psychopathology. During the next fiscal year these findings and those already available will be summarized in a series of articles.

Honors and Awards: None

Publications:

Dent, J. K. and Kwiatkowska, H. Y.: Aesthetic preferences of young adults for pictures drawn by mental patients and by members of their immediate families. Accepted for publication in Science de l'Art - Scientific Aesthetics, 1971.

Serial No. M-AP(C)-15-9
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Systematic Analysis of Brazilian Family Art Evaluations: A Replication.

Previous Serial Number: SAME

Principal Investigators: Hanna Yaxa Kwiatkowska and James K. Dent, Ph.D.

Other Investigators: Dr. Carlos Paes de Barros, Dr. Aroldo Rodrigues, Sylvia Beatriz Valerio Machado, Vera Pollo Flores, Luiz Duprat.

Cooperating Units: Institute of Psychology of the Catholic University in Rio de Janeiro, Brazil, Department of State Committee on International Exchange of Persons (Fulbright Commission).

Man Years:

Total:	0.20
Professional:	0.15
Others:	0.05

Project Description:

Objectives: The overall objective is to explore the differences and similarities appearing in the systematic analysis of pictorial material obtained from Brazilian families with the material obtained from American families, here, in the identically structured situation of the "Family Art Evaluation". The specific objectives are:

(1) To investigate and compare the characteristics of pictures drawn by Brazilian families where a family member has a specific psychiatric diagnosis with the characteristics of pictures of diagnostically similar families in the United States.

(2) To define if eventual differences observed through this analysis could be attributed to cultural variations.

(3) To study the differences in roles of family members in both countries as seen in the different procedures of the family art evaluations.

E.G., in her work with Brazilian families Mrs. Kwiatkowska has observed that the family portraits of Brazilian families frequently include the extended family, thus bringing to light the roles of substitute parents. Is there a correlation between the recurrent inclusion of such substitute parent in family portraits and the degree of pathology in the family? What is the role of the natural parents in such families?

(4) To investigate and compare the interrater agreement on the same items of the rating system in the United States and Brazil. This could also shed light on cultural differences.

Methods Employed: The manual used for the NIMH study was translated into Portuguese by the Staff of the Institute of Psychology at the Catholic University in Rio de Janeiro. It was edited by Hanna Yaxa Kwiatkowska; staff members were trained by her personally to conduct a study parallel to the NIMH study.

A psychologist, Mrs. Vera Pollo Flores, with the consultantship of Miss Sylvia Beatriz Valerio Machado is in charge of the study and under the direction of Dr. Carlos Paes de Barros, Chairman of the Department of Psychology. Other staff members of the Institute were designated as co-ordinators and trainers of the raters. The ratings were done by students as part of their regular curriculum for credit. Dr. Aroldo Rodrigues, Research Psychologist, is a consultant for the statistical aspect of the study.

The patients referred to the Clinic at the Institute of Psychology are mostly children or adolescents in their early teens. Jointly with their families they all have a family art evaluation as part of their routine psychological work-up. A considerable amount of material has been accumulated since the evaluations were introduced there in 1966. In selecting sample families for the present study we were, nevertheless, limited by the age group; we did not want to include families where the index would be less than ten years old. Diagnostically the sample includes families of severely neurotic or behavior problem children, all out-patients at the Clinic.

Major Findings: The ratings of the ten families are completed and cards have been punched in Brazil. The computer analysis to be effected at N.I.M.H. by Dr. James K. Dent will define the findings within the next few months.

Significance to Mental Health Research: Family art evaluations provide a situation which offers a good deal of stability in the manner material is gathered for comparative studies. The basic material (pictures) is collected in an experimental setting structured as identically as possible with the NIMH setting. The methods used for the computer analysis of these data are also identical. The possible flaws in the translation and interpretation of the scoring manual, whether of linguistic or cultural nature are being investigated in a separate study (M-AP(C)-15-10 "Sources of Variance in Cross-cultural Application of an Objective System for Analyses of Pictures

Drawn by Patients and their Families.")

Proposed Course: (1) We must obtain and codify the diagnostic information from medical records of ten investigated Brazilian families. These are to be forwarded to us together with the punched computer cards through the office of the Committee on International Exchange of Persons (Fulbright Commission), the agency collaborating with NIMH in the realization of this project. (2) Computer analysis of this material is to be effected in the course of the summer of 1971. (3) The local Brazilian investigators have to be commended for their increased ability to solve immediate problems through correspondence, which initially presented difficulties slowing down the families of hospitalized adolescent schizophrenic patients is temporarily suspended, because of the difficulties described in last year's report. Upon the completion of statistical analysis of the present sample and depending on the obtained results as compared to the NIMH sample, we may attempt to return to the initially planned investigation of other diagnostic groups.

Honors and Awards: NONE

Publications: NONE

Serial No. M-AP(C)-15-10
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Sources of Variance in the Cross-Cultural Application of an Objective System for Analyses of Pictures Drawn by Patients and Their Families.

Previous Serial Number: SAME

Principal Investigators: James K. Dent, Ph.D. and Hanna Yaxa Kwiatkowska

Other Investigators: Dr. Carlos Paes de Barros, Dr. Aroldo Rodrigues, Sylvia Beatriz Valerio Machado Joffely, Vera Pollo Flores

Cooperating Units: Institute of Psychology of the Catholic University of Rio de Janeiro, Brazil

Man Years:

Total:	0.25
Professional:	0.15
Others:	0.10

Objectives: A system has been developed for objectively classifying pictures drawn by patients and by members of their families in the Family Art Evaluations at NIMH (M-AP(C)-15-8). This rating system which consists of about fifty dimensions has been translated into Portuguese and is being used to describe pictures drawn by mental patients and their families in Brazil, (M-AP(C)-15-1). In application, the two measurements may not be equivalent for several reasons:

(a) Various pictorial symbols may have different significances in culture A (American) from those in culture B (Brazilian).

(b) The English and Portuguese translations may not be equivalent.

(c) Research group A may have particular frames of references not common to their own culture.

(d) Research Group B may also have particular frames of references.

The objective of this project is to begin to sort out some of these various sources of error and variance.

Methods Employed: Sixty-eight pictures selected at random from about one thousand pictures (American families) have been or are being rated as follows:

Ratings 1 and 2:

Two members of research group A have independently rated each of the pictures using the English translation.

Rating 3:

These raters discussed their differences and prepared a check rating representing the best judgment of research group A for each picture.

Rating 4:

Using the English translation, the pictures have been rated by two American college student volunteers working alone (no contact with the research group), each doing about half of the pictures.

Rating 5:

Using the Portuguese translation, a bilingual American college student volunteer rated the pictures alone (no contact with the research group.)

Ratings 6, 7, and 8:

These are like ratings 1, 2 and 3 but are being done by Brizilian members of research group B in Brazil, from slides of the same pictures rated at NIMH.

For the 50 dimensions in the rating system, comparison among these ratings should permit us to isolate translation difficulties and some of the group effects. Presumably differences not attributable to these two sources of variance represent cultural factors in interpretation or individual rater biases. (A study of individual rater biases is included in M-AP(C)-15-8.) Because of the small number of pictures and of having only one bilingual rater, the results will have to be considered tentative. This project is essentially a pilot study for this type of investigation.

Major Findings: The first five ratings above are completed, punched and partially analyzed. We expect to receive the ratings (6, 7 and 8) from Brazil in the near future.

Significance to Mental Health Research: The precise description of mental disorders across cultures is hampered by a paucity of culture-free methods of assessment. Frequently the problem is dealt with by using the inferential judgments of particular clinicians who evaluate patients in two or more cultures. Agreement among them about particular patients is interpreted as constancy in measurement. This system which is biased by language, dialect

and status problems may not provide replicable description; i.e. there are no assurances that another group of clinicians with differing backgrounds would provide the same description, or even a common one.

At the other extreme, one is impressed by the almost universal understanding and appreciation of works of art. The messages of enduring representations of art seem on the one hand to be an expression of the different cultures and on the other hand to convey emotions universally accessible. One is also impressed with the high quality of communication in pure science. Where ideas are precisely defined in observable terms cross-cultural communication is facilitated. For these reasons objective descriptions of art productions may be an important way of achieving cross-cultural communication in the description of mental disorders. In addition to being tangible the communication is not limited and/or biased by the language or dialect problem and the professional has a direct access to the experience of the patient.

Proposed Course: As soon as we receive the ratings from Brazil the analysis can be completed. For dimensions showing a large discrepancy in overall inter-rater agreement an attempt will be made to allocate the differences to one or more of the sources of variance: individual, group, cultural effects or translation differences.

Honors and Awards: NONE

Publications: NONE

Serial No. M-AP(C)-16-1
1. Adult Psychiatry Branch
2. Psychiatric Assessment Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: WHO International Pilot Study of Schizophrenia

Previous Serial Number: M-AP(C)-16-1

Principal Investigator: John S. Strauss, M.D.
William T. Carpenter, Jr., M.D.
Lyman C. Wynne, M.D., Ph.D.

Cooperating Units: John Bartko, Ph.D., Biometrics Branch
Fred Yamada, Laboratory of Applied Studies
Prince Georges General Hospital
Spring Grove State Hospital
Morris Cafritz Memorial Hospital
World Health Organization

Man Years:

Total:	3.5
Professional:	2.5
Other:	1.0

Project Description:

Objectives: (1) To develop standard interview and rating schedules that can be used cross-culturally for the evaluation of psychotic patients. (2) To evaluate a cohort of patients from the catchment area of Prince Georges County, Maryland with these instruments and to compare these findings with similar evaluations being carried out by investigators in eight other psychiatric centers in Colombia, Czechoslovakia, Denmark, Great Britian, India, Nigeria, Taiwan and the USSR. (3) To work toward a concensus with investigators from these other countries about criteria derived from the interview instruments, for classifying patients as schizophrenic. (4) To compare these WHO diagnostic evaluations with clinical evaluations and ratings of the same patients made with other methods such as the Lorr IMPS scale and projective tests. (5) To obtain social and demographic data on patients evaluated by the standard instruments to understand more completely how these factors are related to schizophrenia as defined through the use of the standard diagnostic schedules. These social and demographic data obtained from the NIMH centers will be compared with similar data from the other eight centers participating in the project; and (6) To carry out a follow-up study on patients seen in the original sample to evaluate the course of psychiatric symptoms over a two year period and the course of social functioning over the same two year period.

Follow-up data will be used to amplify and consolidate the information obtained during the initial evaluation for the patients, and to compare the course of psychiatric disorders of different kinds of patients from different countries.

Methods Employed: Initial Evaluations were completed on 135 patients from each center. These evaluations were performed using standardized mental status, history and social description schedules. In this past year, the patients previously seen for initial evaluation were reinterviewed to obtain information on their status at this time, two years after their original episode of illness. Follow-up schedules derived by the investigators from the original standardized schedules were used to obtain these data.

Major Findings: In the past year the semi-final draft of Volume One of the IPSS report has been prepared. This report described methods and findings of the first phase of the IPSS. These phases include 1) the preparation, translation, pretesting, and revision of the data collection instruments; 2) the application of these instruments to 1,202 patients in nine different centers; 3) the evaluation of reliability of the interview schedules, and 4) diagnostic comparisons of the patients seen in the nine centers.

The fact that is was possible to prepare, translate, and revise data collection schedules of this kind with collaboration of psychiatrists from nine centers is in itself a significant contribution of the methodology available to future cross-cultural studies. In evaluating the applicability and reliability of the schedules two findings were especially significant. First, it was possible to use the same standardized mental status interview (in translation where necessary) in all of the collaborating centers and reliability of ratings within each of the centers was high. The reliability of the ratings across centers was moderately high. Although great efforts were extended in evaluating cross-center reliability by having all investigators rate filmed interviews, the methodology of these evaluations was more difficult than originally anticipated and may well have yielded figures somewhat reduced by the difficulties in the reliability testing procedure. Because history and social description data had to be collected in different ways in the different centers and because these data depend so much for their psychiatric dignificance on the cultural milieu, it was more difficult to evaluate the comparability of these kinds of information from center to center. However, the schedules provided a useful means of collecting these data and represent a first step towards the development of comparable methodology in this area as well.

The comparison of similarities and differences in patient types seen in the different centers was given considerable attention. The inherent complexity of such a comparison, even of patients within one center, is often underestimated, but was highlighted by the cross-cultural nature of this project. Three different methods for describing diagnostic types were used. The results of these three different methods were then compared

The first diagnostic method was having the interviewing psychiatrist assign to the patient one of the commonly used clinical diagnostic categories. The categories defined by the International Classification of Diseases were those most frequently used: however, some centers tended to use unusual categories more frequently than others, and a few centers used special diagnostic categories customarily applied only by psychiatrists in their area. Analysis of symptom profiles of the different diagnostic types showed broad similarities across centers for the general diagnostic categories such as schizophrenia, and manic-depressive psychosis. It indicated further that patients with some of the commonly used defining characteristics of these diagnostic categories were seen in all centers. Comparison of symptom profiles to diagnostic labels applied by investigators from the centers also clarified many differences in the way in which psychiatrists from different centers used symptom information in reaching a diagnosis.

A second diagnostic method used to analyze the types of patients seen in this study was a computer program developed to simulate clinical diagnoses as they might be made by the psychiatric school lead by Kurt Schneider. Using data from the mental status examination and psychiatric history, this computer method (Catego) was able to duplicate to some extent the broad clinical diagnoses such as schizophrenia, and psychotic depression given to the patients by the investigators in the centers. This method represents considerable progress in developing a technique for applying diagnoses to patients which can be applied in different centers with complete reliability.

The third method used for assigning patients to diagnostic categories, employed cluster techniques. With these mathematical techniques for defining groups of patients, it was possible to arrive at categorizations that wer somewhat similar to both clinical and Catego diagnoses. The cluster techniques also provided a means for defining certain subgroups of patients that were seen in only one of two centers. The results of these three methods were compared and combined to describe basic similarities and differences among the patients seen in the different centers.

The data from the study is also being used as source for other closely related investigations: (M-AP(C)-16-3, M-AP(C)-16-4). These studies involve more intensive investigation of certain aspects of the data obtained during the IPSS and comparison of these data with similar information obtained from other sources.

Significance to Mental Health Research and the Program of the Institute: The difficulty in comparing psychiatric patients from different cultures has made it impossible to evaluate accurately the etiological importance of cultural factors in psychiatric disorder. The absence of standard methods for evaluation and diagnosis of psychiatric patients has also made it difficult to compare incidence and prevelance rated in different cultures and to compare usefulness of treatment methods employed in different centers. Until such can be performed, it is not possible to test many

crucial hypotheses regarding the nature and etiology of psychiatric disorders. The difficulties in establishing standard instruments are considerable, not only in the writing and testing of such instruments but in the extensive negotiations and communications necessary with the various investigators from different countries with diverse backgrounds and orientations. Nevertheless, in this study it has been possible to develop such instruments that can be applied in a useful way in a variety of cultural settings. These instruments were used with patients in nine different countries and proved to be applicable and useful for this purpose.

While methods of evaluating patient characteristics must be developed in order to perform cross-cultural studies, it is also essential to develop methods for categorizing patients once their characteristics have been elicited and rated. In the current studies, three different methods were used to categorize patients and to compare patient types among the different centers. Through applying these methods it is possible to show in what sense patients seen in the different centers are similar and in what sense they are unique. The combinations of these methods can also be used to determine in what sense the statement "schizophrenia is found in all of the nine centers: is true, and in what sense the statement omits recognition of real differences of "schizophrenic" patients from the different centers.

The completion of a follow-up study on the patients originally interviewed adds the crucial dimension of course of illness to the evaluation. By having standardized, comparable information on patients from different countries at two points in time it will be possible to compare course of illness cross-culturally and to investigate further the use of outcome of psychiatric illness to validate the original diagnoses.

Proposed Course of the Project: In the coming year the data from the follow-up phase of the IPSS will be analyzed and preparation of Volume Two of the IPSS report will be undertaken. The usefulness and reliability of collecting follow-up data with the methods used in this study will be evaluated. An evaluation of course of illness in different centers will be performed to study the relationship of course of illness to culture and to diagnostic category.

Besides participating in the basic aspects of the IPSS, our center will continue to use the data to compare with similar data obtained in different groups of patients seen in the Clinical Center (M-AP(C)-16-3) and other psychiatric facilities. Data that has been obtained using the International Pilot Study of Schizophrenia standard schedules will be compared with data obtained from psychological procedures, Rorschach tests, and the In-patient Multidimensional Psychiatric Scale (Lorr).

Publications: Strauss, J.: Reliability and Applicability of the Assessment Instruments Used in The International Pilot Study of Schizophrenia. To appear as a chapter in the International Pilot Study of Schizophrenia, Volume One, WHO, Geneva, Switzerland.

Strauss, J.: Empirical Methods for Grouping Psychiatric Patients. To appear as a Chapter in The International Pilot Study of Schizophrenia, Volume One, WHO, Geneva, Switzerland.

Honors and Awards: None

Serial No. M-AP(C)-16-3
1. Adult Psychiatry Branch
2. Psychiatric Assessment Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Manic-Depressive Psychosis-Schizophrenia Comparative Studies

Previous Serial Number: M-AP(C)16-3

Principal Investigators: William T. Carpenter, Jr., M.D.
John S. Strauss, M.D.

Other Investigators: Lyman C. Wynne, M.D., Ph.D.

Cooperating Units: John Bartko, Ph.D., Biometrics Branch, Fred Yamada, Laboratory of Applied Studies, NIMH, Prince Georges General Hospital, Spring Grove State Hospital, Morris Cafritz Memorial Hospital, World Health Organization, 3-E and 4-W Nursing Units, Clinical Center, NIH, Section on Psychiatry, Laboratory of Clinical Science.

Man Years:

Total:	0.3
Professional :	0.2
Others:	0.1

Project Description:

Objectives: (1) To utilize standard interview and rating schedules to collect data on manic-depressive patients. (2) To utilize this data and data collected on a larger group of schizopnrenic patients in a comparable manner to investigate similarities and differences in symptomatology within these diagnostic categories. (3) To provide a sufficiently large sample of manic depressive patients to enable comparison with similarly diagnosed patients from other field centers in the WHO International Pilot Study of Schizophrenia. (4) To provide baseline data so that follow-up evaluation can be carried out in order to gain more systematic information regarding the course of manic-depressive illness. (5) To obtain data with which to test the hypothesis that many of the usually accepted criteria for a depressive illness (i.e., biological signs, psychosomatic complaints, sleep difficulties, decrease in libido, etc.) do not have high order discriminatory function between depression and other forms of mental disturbances. (6) To generate a sufficient sample of depressed patients to explore the hypothesis that a diagnosis of schizophrenia is often used for a person who otherwise is comparable to a psychotic depression but has a bizarre delusion or the presence of an hallucinatory phenomena which many clinicians in practice do not identify as part of a depressive illness. (7) To elucidate the concept of schizo-affective schizophrenia by examining the signs and symptoms present in cases so diagnosed comparing them with

depressed patients and schizophrenic patients during illness and through a follow-up period.

Methods Employed: The standard instruments were developed for the WHO International Pilot Study of Schizophrenia. They were developed, revised, and extensively pretested on at least 24 patients from centers in eight countries and have been used in the past year on a cohort of 135 patients from each center. Four basic interview forms comprise the standard instruments and are described in project No. M-AP(C)-16-1. Using these schedules on a sample of patients not included in the IPSS, 37 manic depressive patients have been interviewed from wards 3-E and 4-W in the Clinical Center, NIMH. Computerized statistical methods are being developed to analyze the data collected from these groups of patients to develop empirical "clusters" of patients based on the symptoms they demonstrate. In addition the material on certain sub-groups of patients (i.e., schizo-affective schizophrenia) will be examined by the principal investigators in an effort to clarify descriptive and conceptual aspects of the diagnostic categories.

Major Findings: During the past year 135 patients have been seen in the Bethesda center of the IPSS of whom 4 have been diagnosed as manic-depressive, psyhcotic depressive, or neurotic deprevvise. In addition some 37 patients with this diagnosis have been interviewed in the Clinical Center. Follow-up interviews of manic-depressive patients will be carried out during the coming year.

Significance to Mental Health Research and the Program of the Institute: There is a paucity of data using standardized interview techniques comparing manic-depressive patients and schizophrenic patients. Evaluating these two diagnostic groups and comparing them with similar groups from the various field centers in the WHO International Pilot Study of Schizophrenia offers an opportunity to clarify the use of misuse of the diagnostic categories and to describe more clearly phenomena represented in each and the distinguishing features of the various diagnostic categories.

Proposed Course of the Project: During the coming year the development of analytic tools to evaluate the data will be carried out and analysis of the data will be started. Follow-up interviews will be conducted. It is anticipated that by applying clustering techniques to the data collected with the standardized assessment tools that we will be able to identify patients who are similar and to describe crucial points of distinction between groups that will enable us to understand better the diagnostic process and possibly to refine the basis for diagnostic categories. Cross-cultural comparisons of patients and psychiatrist, especially with Denmark will be undertaken.

Honors and Awards: None

Publications: None

Serial No. M-AP(C)-16-4
1. Adult Psychiatry Branch
2. Psychiatric Assessment Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Empirical Grouping of Psychiatric Patients

Previous Serial Number: M-AP(C)-16-4

Principal Investigators: John S. Strauss, M.D., John Bartko, Ph.D., William T. Carpenter, M.D.

Other Investigators: Fred Yamada

Cooperating Units: Prince Georges General Hospital, Spring Grove State Hospital, Biometrics Branch, NIMH, Computer Center, NIH, Cafritz Memorial Hospital, World Health Organization

Man Years:

Total:	0.6
Professional:	0.4
Other	0.2

Project Description:

Objectives: (1) To develop methods for grouping psychiatric patients empirically. (2) To determine whether patients as defined by their symptoms fall into natural groups. (3) To help clarify the extent to which the grouping of psychiatric patients imposes groupings on a sample that varies along continua and does not fall naturally into discontinuous groups. (4) To evaluate factoring methods commonly used for the empirical grouping of patients.

Methods Employed: In the process of analyzing the data generated by the WHO IPSS [M-AP(C)-16-1] some difficulties with commonly used clustering and factoring procedures for grouping patients became apparent. In an attempt to develop more satisfactory techniques it was important to identify the source of these problems. The investigators have used a series of different statistical techniques to locate where in the process of data analysis the difficulties arose. To accomplish this both the patients seen in the WHO IPSS and a group of 100 "typical" patients whose ratings were fabricated by the investigators were used as "subjects". Different methods of factor analysis and cluster analysis were used to group these patients. In this process one procedural variable was changed at a time so that key variables could be identified.

Major Findings: In the course of this work it has become clear that the results of the commonly used clustering and factoring techniques for grouping psychiatric patients are much less stable than is generally recognized. A

typical output of groups that "looks good" on inspection will be totally rearranged by the change of just one or two minor variables such as the adding of a few patients or a slight change in the cut off point determining which items are to be included in loading on factors. The instability of the output of these techniques raises questions regarding their usefulness. It has been possible to identify the variables that are significant in changing outputs and at the same time to identify those variables such as the type of cluster programs that give clusters that are more stable.

Significance to Mental Health Research and the Program of the Institute

Because of the unreliability of psychiatric diagnoses and their limited utility, many investigators have turned to mathematical models to define more meaningful groups of psychiatric patients. These efforts may one day be important in defining groups of patients with similar causes and courses of their disorders and similar responses to treatment and thus provide considerable progress in research, treatment, and prevention of psychiatric disorders. The mathematical models currently in use have many weaknesses that must be recognized and eliminated before such a step can take place. By comparing different methods of data analysis with the same group of patients, we are currently identifying some of these weaknesses and concurrently attempting to develop a more useful technique of data analysis with more meaningful and stable output.

Proposed course of the Project: The work completed thus far is being prepared for publication. Further efforts continue along two major directions: 1) the use of different programs to define more of the problem areas and to develop more satisfactory methods for grouping patients; 2) an alternate direction, the developing of dimensions of psychiatric function for identifying psychiatric patients rather than attempting to place patients into discrete groups. This effort stems from the hypothesis generated from the study, that it might be impossible to define groups of patients empirically not because of the methods used but because these patients don't in fact define natural groups and are more suitably represented as defining points on continua of psychiatric and psychological function.

Honors and Awards: None

Publications: None

Serial No. M-AP(C)-16-5
1. Adult Psychiatry Branch
2. Psychiatric Assessment Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Serum Enzymes in Acute Psychotic States

Previous Serial Number: M-AP(C)-16-5

Principal Investigators: John S. Strauss, M.D.; Herbert Meltzer, M.D.; William T. Carpenter, Jr., M.D.

Man Years:

Total:	0.2
Professional:	0.1
Others:	0.1

Project Description:

Objectives: In an attempt to determine relationships between biochemical findings and psychotic conditions, Dr. Meltzer has demonstrated that creatine kinase and serum aldolase levels are often elevated in acute psychotic states. The objective of this project is to determine more precisely in which psychotic conditions these enzymes are elevated and in which conditions they are not. By the use of standardized diagnostic interviews to obtain information on a wide variety of symptoms and environmental conditions it will be possible, using a sample of patients to define more clearly the correlations of individual symptoms with enzyme elevations and the relationship between duration of symptoms and enzyme elevation. Since a wide variety of patients will be seen it will be possible to re-evaluate how reliably these enzyme methods differentiate schizophrenic patients from other psychotic and borderline conditions.

Methods Employed: A series of patients will be interviewed using standardized mental status, history and social description interviews. Blood will be drawn at the time of the mental state interview and analyzed employing methods currently in use by Dr. Meltzer for determining serum aldolase and creatine kinase.

Major Findings: A pilot sample of patients was tested with the techniques described. Only one of these demonstrated significant elevation of the enzymes being measured, but these negative results were considered

possibly to be the result of the rapid drop in serum enzymes following hospital admission. In spite of considerable effort it has not been possible at other psychiatric facilities to obtain serum as early as required. In the series of patients to be seen at the clinical center rather than at other facilities as previously attempted, blood will be drawn on the day of admission to control for the possibility of the sudden decline in enzymes following admission.

Significance to Mental Health Research and Program of the Institute: There is much interest in determining whether schizophrenia and other psychotic conditions can be related to particular biochemical and other physiological measures. Although there is some evidence for such relationships in regard to certain affective psychoses, evidence for similar relationships in schizophrenia is more controversial. Dr. Meltzer has been able to demonstrate relationships between creatine kinase and serum aldolase in psychotic conditions but it is not clear yet to what extent elevations in these enzymes are related to (1) the acuteness of the psychotic conditions, and (2) particular clinical pictures, including symptom and pre-morbid patterns. In the present study, it will be possible to help clarify some of these relationships as well as to evaluate by replication Dr. Meltzer's earlier work.

Proposed Course of the Project: A series of patients will be interviewed and their serum enzymes analyzed. On completion of the data collection, symptom patterns and psychiatric history events will be compared to the results of the enzyme determinations to see whether a meaningful relationship exists.

Honors and Awards: None

Publications: None

Serial No. M-AP(C)-16-6
1. Adult Psychiatry Branch
2. Psychiatric Assessment Section
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychiatric History Study: The Nature and Reliability of the Data

Previous Serial Number: M-AP(C)-16-6

Principal Investigators: John J. Strauss, M.D., William T. Carpenter, Jr., M.D.

Other Investigators: Ruth E. Boesman, R.N.

Cooperating Units: John Bartko, Ph.D., Biometrics Branch, Nursing Units, 4-E, 4-W, 3-E, 4-W, NIH, Clinical Center

Man Years:

Total:	0.1
Professional:	0.07
Others:	0.03

Project Description:

Objectives: (1) To identify different types of data ordinarily obtained in psychiatric history interviewing. (2) To study the reliability for these data as obtained from the patient compared to that obtained from his relative. (3) To study the effect of when in the course of hospitalization data is obtained on the nature of the data elicited. (4) To learn how psychiatric history is obtained in various psychiatric settings. These data will be used to examine the hypothesis that there is a greater variability in psychiatric history information than is usually expected and that the nature of the data obtained relates to the degree of variation.

Methods Employed: Standardized psychiatric history and social description interview schedules developed for the International Pilot Study of Schizophrenia were utilized in interviewing. The first 20 admissions to one of the psychiatric nursing units who also had relatives available as informants were interviewed. The patient and relative were interviewed within one week of admission and again six weeks later. The same interview schedules were used in each interview and the interviewing was rotated between the three investigators listed above in an effort to keep the interviewer as naive as possible to patient information other than that obtained during the interview.

A questionnaire was sent to a large number of facilities that admit psychiatric patients in the United States. This questionnaire requested information about who interviews whom and at what time to obtain psychiatric history information. Data has been collected from 20 patients and their relatives and is being analyzed to determine reliability. Narrative summaries of the interviews and certain key items will be examined by the investigators in order to determine comparability of the less structured aspect of psychiatric history evaluation.

Major Findings: During the past year twenty patients and their relatives were interviewed. Tabulation and analysis of the data is being carried out.

Significance to Mental Health Research And The Program of the Institute: The relationship of past experience to present behavior is fundamental to most psychological theories of behavior and mental function. There is a paucity of data testing the reliability and validity of background information obtained from psychiatric patients and their families. This study will attempt to identify the various means of collecting past history from psychiatric inpatients in various settings and to identify the pitfalls involved in interpreting this information.

Proposed Course of the Project: During the coming year the data analysis will be completed and reported.

Honors and Awards: None

Publications: None

Serial No. M-AP(C)-17-1
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: A Study of Problems in Growth and Adaptation in the Personality Development of the Adolescent

Previous Serial Number: NONE

Principal Investigator: Roger L. Shapiro, M.D.

Other Investigators: Carmen Amoros-Cabrera, M.S.W.; Stuart Hauser, M.D.; Kent Ravenscroft, M.D.; Sheldon Roth, M.D.; Winfield Scott, Ph.D.; and John Zinner, M.D.

Cooperating Units: Unit 3-West

Man Years

Total: 3.90
Professional: 3.30
Other: .60

Project Description:

Objectives. The ongoing foci of study in this project are family studies and peer and authority relations and the place these play in adolescent development. The core observations of the individual adolescent and the behavior of his family are now supplemented by regular observation of his relationships in the residential treatment unit.

Methods. This year more formal study of the residential treatment unit itself has been done through formation of the Unit Study Group. This is a weekly, hour-long meeting which is observed and tape recorded. It is conducted by Dr. Roger Shapiro, the clinical director of the unit; Miss Gay Grover, the chief nurse; and Dr. Kent Ravenscroft, the unit administrator. All of the patients living on the unit attend this meeting. Its purpose is to study the relationship of the adolescent patients to adults in authority roles as well as their relationships with each other. In this meeting roles the adolescents take and are given by their peers and in relation to authority figures are explored and articulated. These are compared to roles the adolescents take and are given in their families. The range of behaviors seen in the unit study group and the family group are compared to similar observations made on normal adolescents at Sidwell Friends School.

Unit 3-West continues to be a residential treatment for adolescents. Criteria for admission include age (14-21 years), participation of parents and adolescent siblings in family therapy, and pathology in the index including the range of non-psychotic disturbances of adolescence. Typical problems experienced by these adolescents prior to their admission include frequent drug use, especially marihuana but including LSD; running away; deteriorating school performance and truancy; impulsive behavior; and depression with suicide attempts.

Our methods for study of the family continue to utilize transactions in ongoing conjoint family therapy. In general, we study intact families, although we continue to work with a few patients from broken families. We work with the parents and any adolescent siblings in addition to the index patient in weekly conjoint family therapy. A weekly marital therapy session is routinely done, generally by Mrs. Cabrera, our psychiatric social worker. The adolescent is also seen three or four times a week in individual therapy. The family cotherapists are generally the psychiatrist treating the adolescent and the social worker treating the parents.

This combination of therapies provides the data from which we formulate the disturbance in ego functioning and identity of the adolescent and the dynamics of family group process which we hypothesize is related to the disturbance in individual functioning. We continue to organize our observations around the concept of delineation. This requires us to formulate explicitly the views, images, or attitudes one family member holds of another, to consider the dynamics of these delineations and particularly their defensive utility, and to consider their consequences for the family member being delineated. Dynamics of delineations and their formal characteristics are the data from which we formulate characteristics of the family as a group. We then consider the relation of these family group characteristics to disturbance in the individual adolescent.

The unit study group provides us with a view of the adolescent in a group situation outside of his family where he must relate to his peers and to adults in authority roles other than his parents. Behavior of the adolescents in the group is compared to their behavior with their families and contrasted to the functioning of normal adolescents at Sidwell Friends School.

Major Findings. A central finding in our work with disturbed families is that parental delineations are more frequently determined by the parent's own emotional and defensive needs than by realistic perceptions of the adolescent's personal and individual qualities. The dynamics of delineations in these families, particularly their frequent origin in projective identification, and the formal characteristics of delineations, particularly in disturbances in cognition in transactions containing defensive delineations, are all being explicated in the families we are studying. The relation of these elements to the characteristics of the family as a group and to outcome in the individual adolescent is being reported by Drs. Shapiro and Zinner.

Significance to Mental Health Research. This study now includes methods and findings for studying the adolescent peer group as well as studying the adolescent and his family. With these methods we will more fully comprehend adolescent personality development from the perspective of identity formation. Our findings thus far clearly indicate that the presence of impaired development of adolescent ego autonomy reflects impaired parental ego functions. We want to consider in what ways and to what extent the peer group can be used to alter and mitigate deleterious consequences of family relationships. We are interested in the implications of these findings both for the highly important task of deepening our understanding of disturbance in adolescence and for improving our techniques of therapy and rehabilitation.

Proposed Course of Project. As has been discussed above, the recording and detailed study of the adolescent patient group and the integration of findings from that group with findings elucidating the adolescent's role in his family is the newest emphasis in our work. In the next year we will continue the comparison of disturbed and healthy adolescents in family interaction and in interaction with their peers in the Unit Study Group and in a classroom study group at Sidwell Friends School.

Honors and Awards:

Roger L. Shapiro, M.D., Principal Investigator:

Director, Group Relations Conference, sponsored by The Washington School of Psychiatry and the Tavistock Institute of Human Relations, Amherst College, August 28 - September 2, 1970.

Senior Staff, Conference on Authority and Leadership, sponsored by the Centre for Applied Social Research of the Tavistock Institute of Human Relations, London. University of Leicester, England, March 26 - April 8, 1971.

Senior Staff, Group Relations Conference, sponsored by The Washington School of Psychiatry and the Tavistock Institute of Human Relations, Mount Holyoke College, June 5-18, 1971.

Presentations:

Roger L. Shapiro, M.D., Principal Investigator:

"The Study Group as Training for Group Psychotherapists." Panel on Group Participation in the Training of Group Psychotherapists, Annual Meeting of the American Group Psychotherapy Association, February 5-6, 1971, Los Angeles, California.

with John Zinner, M.D.:

"Adolescence and the Family" and "Projective Identification as a Mode of Perception and Behavior in Families of Adolescents." Panel

Group Studies in Progress: Adolescent Development from the Perspective of Family Studies, Annual Meeting of the American Psychoanalytic Association, April 29 - May 3, 1971, Washington, D. C.

Serial No. M-AP(C)-17-2
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Adolescent Ego Development in Normal Families

Previous Serial Number: NONE

Principal Investigator: Roger L. Shapiro, M.D.

Other Investigators: Stuart Hauser, M.D.; John Zinner, M.D.

Cooperating Units: Sidwell Friends School, Washington, D. C.

Man Years:

Total: .7
Professional: .6
Other: .1

Project Description:

Objectives. This study attempts to specify some of the crucial determinants of identity formation in normal adolescents. We hypothesize that delineations of the adolescent by his family and his peer group provide much of the content of his self concept and that the manner in which the delineation is communicated will influence the way in which it is internalized. We further hypothesize that the adolescent will utilize peer group experience in an attempt to reorganize conflicting elements in his self concept which have derived from conflicting elements within his family. We hope to specify in detail in what ways peer group experience allows for development of new and innovative aspects of identity and in what ways it is conditioned and limited by past and present family interactions.

Methods Employed. During this year a Classroom Study Group was formed at Sidwell Friends School. This group was composed of 10 students, ages 12-14, in the seventh grade of the Sidwell Middle School; their teacher, Mrs. Carter; their principal, Mr. Arnold; and Dr. Stuart Hauser as group consultant. The task of the group was to study authority relations and peer relations in the classroom, making observations about group formation, individual roles in the group, relations to authority in the group as we have with the Unit Study Group on the adolescent inpatient unit. Particular attention was paid to the capacity of these adolescents to define themselves verbally in relation to authority figures and peers. The range of attitudes toward self and others and capacity to tolerate differences and to work with

the boundaries established by authority were foci of attention. The group met for 14 weekly sessions of an hour each.

In addition, Dr. Hauser worked with four other adolescent groups of four sessions each at the Sidwell School discussing identity themes in order to generate data for comparison to the patient population in a longitudinal assessment of identity formation (Project M-AP(C)-17-5).

Major Findings. In the Classroom Study Group far less anxiety and inhibition was seen in group function and activity than was seen in the Unit Study Group. The students were quickly highly verbal and involved in clearly defined ways. The principal and the teacher had difficulty representing their actual school roles in the group and still feeling a part of the group. Their presence focused much of the group's attention on authority relations although explicit discussion of attitude toward teachers and school administration was far less common than expression of implicit attitudes. The Classroom Study Group demonstrated the feasibility of such a group in the Sidwell School setting. The school found the group useful and has invited us to do a similar group next year in the Upper School. We are interested in this because the age of the Upper School children, 14-17, would offer a better comparison to our patient group.

Significance to Mental Health Research. The study of peer relations and of family relations of normal adolescents provides a contrast to our studies of peer relations and of family relations of disturbed adolescents. This increases the precision of our formulations of the pathological processes in adolescent disturbance and thereby contributes to a better understanding of the etiology of adolescent personality disorder. At the same time the study provides data on the ways in which peer and school experience contributes to normal identity formation and thereby contributes to an understanding of normal development.

Proposed Course of Project. Next year we want to repeat the Classroom Study Group with older adolescents for more detailed comparison to the Unit Study Group. We also want to do more conjoint family interviews with these adolescents and their families for comparison with our patient sample.

Serial No. M-AP(C)-17-3
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies of Psychogalvanic Response in Family Therapy

Previous Serial Number: NONE

Principal Investigator: John Zinner, M.D.

Other Investigators: David Reiss, M.D. and Roger Shapiro, M.D.

Cooperating Units: Experimental Group and Family Studies Section, APB; Unit 3-West

Man Years

Total: 1.25
Professional: .50
Other: .75

Project Description:

Objectives: The family psychophysiology project was initiated to provide quantifiable information about subjective experience during family interaction that would supplement self reports of family members and inferences made from observable behavior.

Studies of interaction in families of emotionally disturbed adolescents carried out by this section in the past and concurrently have consistently focused attention on the subjective experience by family members of one another as important determinants of family group behavior. In particular, we have found clinically that family members often behave in such a way as to reduce anxiety in the family group as a whole or within particular members. In the case of emotionally disturbed adolescents the psychopathologic outcome may derive at least in part from the patient's attempts to diminish parental anxiety over parental intrapsychic conflict.

Because family members may not be aware of anxiety during family sessions and because anxious members may choose to remain silent and not report their feeling or demonstrate it overtly in their behavior, we undertook to monitor continuously autonomic indicators of anxiety during family therapy sessions. The study therefore adds a psychophysiologic dimension to our ongoing investigations of the interplay between subjective experience and behavior in family interaction. Since the unit of study is conjoint family

therapy, an opportunity is provided for exploration of the process of family therapy within individual sessions and on a long term basis, as well as the physiologic reactions of family members to the interventions of the psychotherapists.

Method. The sample consists of families of adolescent patients admitted to our treatment program as well as families of "normal" adolescents interviewed in the "Sidwell Project."

The psychophysiologic variable selected for initial study was the galvanic skin response (GSR) which is known to be a rather good indicator of anxiety occurring in an interpersonal context. In addition, the GSR has the value of being discrete, unidirectional, easily visualizable and proportional in amplitude to the experienced intensity of the emotional stimulus.

During conjoint family interviews, the GSR of family members and therapists are monitored continuously on a Grass Polygraph by way of electrodes attached to two fingers of each subject's non-dominant hand. A timing device and polygraphic recording of speech permits the accurate synchronization for retrieval of physiologic responses and concurrent verbal behavior. In addition, sessions may be video-taped using a split-screen technique which records and displays simultaneously both the family in interaction and the polygraph record. Playback of these videotapes permits an analysis of the sequential unfolding of family behavior and subjective experience of family members.

Progress and Findings. During the past year, attention has been focused on analysis of previously obtained data from three "disturbed" and one "normal" family.

Close scrutiny of split-screen video tape recordings from one family of a "borderline" adolescent girl indicate that psychological defenses, such as denial and projection, are effective in suppressing autonomic responses, insofar as the GSR is concerned. The index patient is seen to be physiologically responsive to maternal anxiety and to initiate "rescuing" behavior which reduces the frequency and amplitude of GSR's both within her and her mother.

Study of records from three other families support the notion of the effectiveness of psychological defense in suppressing vegetative responses. The variable success of these defenses can in fact be graded in terms of their ability to limit physiologic reactivity. Furthermore, it appears that individuals who have been regarded in previous experimental studies to be electrodermally "unreactive" will react strongly if a sufficiently intense emotional stimulus is presented, such as may be generated in family therapy. Thus the relative lack of GSR activity found in some subjects by other investigators may be a product of effective and potent psychological defense mechanisms rather than a result of idiosyncratic neurophysiologic givens. Study thus far of the interventions of family therapists suggest that the

intensity of the family member's physiologic responses are determined more by the relevance of the psychotherapist's interpretations to immediate interpersonal or intrapsychic conflict than to the apparent "depth" of the psychological intervention.

From our observations it appears that behavior of family members may frequently "organize" around interactions of high emotional valence in such a way as to diminish the intensity of the emotional experience by the use of interpersonal defenses, withdrawal or distracting maneuvers.

During the past year, efforts have also been directed toward reducing the considerable amount of data for statistical analysis. In particular, a successful attempt has been made in developing a computer program which retrieves physiologic data on family members occurring within specifiable categories of individual or family behavior. Our first analysis has involved the examination of physiologic reactivity of family members during periods in which specific dyads are speaking or listening to one another. From the analysis of the family of a "borderline" adolescent, we have found that the intensity of physiologic reactivity of any given family member or therapist does not occur randomly, during the session, but is dependent upon the identity of the family member with whom he or she is interacting at the moment. Comparisons across two sessions of this family monitored only a few weeks apart reveal that changes in the physiologic reactivity of family member A, while in interaction with family member B, are accompanied by parallel changes in the reactivity of family member B while in interaction with A. A less exacting examination of another family sampled over a prolonged period of psychotherapy suggests that these patterns of physiologic reactivity may be modified by the treatment process in a direction that conforms with clinical observation.

While attempts to score, retrieve and graphically represent data have been successful, the findings noted above are tentative and limited to a very few families. Nevertheless, the results lead us to be optimistic about the value of using psychophysiologic measures in family interaction both as a source of information about family process and the result of extrafamilial intervention in modifying the quality of family interaction and inter-experience.

A further finding arising out of the statistical analyses concerns the relative independence (with a few possible exceptions) of measures of the amplitude of GSR from the prestimulus basal skin resistance within individuals. This finding is at variance with several other studies supporting the interdependence of these two measures. Our results, in addition to their relevance to psychophysiologic investigations, may greatly simplify our procedures of statistical analysis.

Serial No. M-AP(C)-17-4
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: A Follow-Up Study of 37 Families Treated in the Study of Adolescent Identity

Previous Serial Number: M-OD-CI-SW-9(c)

Principal Investigators: Carmen Amoros-Cabrera, M.S.W., Roger Shapiro, M.D.

Other Investigators: Sheldon Roth, M.D.

Cooperating Units: Nursing Unit 3-West

Man Years:

Total: .60
Professional: .40
Other: .20

Project Description:

Objectives. To obtain information about the current adjustment of the adolescent and his family as related to (1) the problems that motivated their admission to the project, and (2) their individual perceptions of the effects of therapy and the relationship of therapy to any changes that may have taken place.

Methods Employed. The family group, the adolescent, and the parents are seen in separate interviews with the goal of providing information which will allow for the isolation and identification of various factors comprising the therapeutic experience, such as the impact of the adolescent's hospitalization, ward milieu, family therapy, couples therapy, and individual therapy. The outcome of each aspect of the therapeutic program is emphasized, and outcomes will be evaluated for a number of categories still being defined.

Progress. Nineteen families have been seen in the follow-up study, and from discussion of their experiences interview techniques have been modified to augment the amount of data obtained. A number of the remaining eighteen families have been contacted and will be seen within the coming year.

Significance for Mental Health Research. We are particularly interested in learning about the success of the therapeutic plan in clarifying the index patient's identity problem and in understanding and modifying the parents' delineations of the adolescent. This study will be useful in isolating factors contributing to the precipitation of serious adjustment problems during adolescence and in evaluating the outcome of a treatment program derived from research findings.

Proposed Course of Project. Plans are being made to interview the remainder of the 37 families scheduled for follow-up and to begin analyzing the material from the follow-up interviews. Categories for evaluation of the impact of therapy and outcome of treatment are still being refined.

Honors and Awards: None

Publications: None

Serial No. M-AP (C)-17-5
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Cognition and Identity Development in Early and Late Adolescence: Longitudinal Studies

Principal Investigator: Stuart T. Hauser, M.D.

Other Investigators: Roger L. Shapiro, M.D.

Cooperating Units: Ward 3-West, Normal Volunteer Office

Man years:

Total: .50
Professional: .30
Other: .20

Project Description:

Objectives. An earlier longitudinal study of identity formation in lower socio-economic class boys (Hauser, S.T., Black and White Identity Formation, N.Y., Wiley, 1971) suggested several areas for further investigation. A clear difference in identity formation patterns was found between the black and white adolescent subjects. Among the questions of interest emerging from this earlier investigation were:

1. Do the divergent identity patterns found for these black and white adolescents also reside in other, larger, population of such social and racial characteristics?

2. What are the variants of identity formation in other adolescent groups, such as middle socio-economic boys and girls, late adolescents, psychiatrically hospitalized adolescents?

3. What are other aspects of psychological functioning which are associated with varying identity formation patterns? In particular, cognitive processes appear to be related to modes of self-image perception. How then are these cognitive areas linked with identity development patterns, more complex patternings of self-images? Are certain cognitive or perceptual processes more powerfully linked to identity development?

It was with these questions in mind that the current studies were designed.

categories generated by a subject; and, in addition, analyze his reasons underlying his categories (conceptualizations)

d. The Twenty Questions Task. To measure the type, and degree of efficiency of a subject's problem solving strategy.

e. Draw-a-Person Task. The drawing of persons obtained will be analyzed using the scales devised by Wilkin and Associates for measurement of "sophistication of body image," a variable highly associated with differentiation.

Steps "2" through "4" will be repeated every six months for a two-year period. Thus each subject will be interviewed and tested a total of five times.

The measurements which are being obtained from these instruments include correlational indices, general measures of relatedness and of discrimination (all obtained from the Q-sorts); indices of the sources of self-image components (also from the Q-sorts); specific cognitive variables from each of the cognitive instruments noted above.

Techniques for analyzing the complex data will be along several lines in order to investigate inter-relationships of the variables at single points in time, and over time; and to investigate consistencies within individual subjects and between groups of subjects. Two basic statistical tools will be analyses of variance and factor analyses. Both these approaches and their implementation are being worked out with Dr. John Bartko, statistical consultant, and the computer center.

Major Findings. At this point the first wave of interviews and testings have been completed on most of the controls and patients. In fact, we are now preparing for the second time sample for most of these subjects. Several patients and controls have already been seen and tested for the first six-month follow-up. The data obtained from the first round is currently being analyzed for the measures noted earlier. Correlational analyses of the Q-sort data are completed.

A second aspect of the sample is the black-white comparative studies. The new group begun in Boston is now being seen for the second year. Data from an older sample from New Haven is being re-analyzed using new tools: information statistics (for analysis of structural complexity of self-image and over-all relatedness) and drawing analyses for study of differentiation. The structural complexity analysis of the older longitudinal data is now essentially completed and is consistent with lessened structural complexity (more polarized) self-image for several of the blacks' images.

Significance to Mental Health Research. These studies are directed toward an increasingly intensive analysis of self images from several perspectives: Their "inner characteristics of meaning and structure, their relation to one

Methods Employed. To approach the preceding questions several populations of subjects are being sampled:

1. Matched lower socio-economic class black and white adolescent boys (36 subjects).

2. Adolescent male and female patients of middle socio-economic class background (24 subjects).

3. Adolescent male and female high school and early college age students, also of middle socio-economic class status (35 subjects).

Each of the subjects from these samples will be studied longitudinally for two years, being seen every six months. The sequence of meetings and instruments used, with rationale for their use is the following:

1. Groups of seven to eight subjects from each of the samples will meet with the senior investigator for a series of four meetings, focused around "the study of roles and perceptions of the self and others in the group".

2. From the tapes of these meetings, a separate Q-sort deck will be generated for each group. The deck will consist of 3x5 cards, on each being an "I" statement made by a group member which reflected a particular personal emotional, ideological or general descriptive position about himself. There will be an equal number of statements from each group member, ncluding the leader.

3. Each subject will be individually interviewed following the conclusion of the four group meetings. The thrust of the individual sessions will be around self-conceptions, current and past. Inquiry will also be along the lines of developmental and family history.

4. The following week the subject will take the Q-sort task. In this method he will be asked to sort the deck from his group (described in #2 above) for a series of seven different self-images. These include self-images for the present, in the eyes of friends; in the future, in the past. There are a total of seven self-images, always requested in the same order by the experimenter.

5. In the following testing one to three weeks after the Q-sort, the subject will be tested with a series of cognitive measures. The techniques, their rationale and their order of being taken are:

   a. The Pettigrew Category Width Scale. This is to measure the breadth or narrowness of a subject's categories

   b. The Concealed Figures Test. For determination of degree of field articulation, of "differentiation".

   c. The Object Sorting Test. To determine the size and number

another, their modes of change over time, their relation to other modes of personality functioning which appear highly relevant such as cognitive processes. One important application of such quantitative studies is as a means of following the course of an adolescent during psychotherapy comparing other measures with independent observations, such as those of nurses or the patient's therapist. A second application is to the comparison of adolescent development with and without psychotherapy, and under different modes of psychotherapy (half the patient population is receiving only group therapy, the other half is in group and individual therapy).

The operationalizing of major concepts such as "identity formation" and "psychosocial moratorium" is still a third important consequence of this kind of research. Through such operationalizing the concepts are given clearer empirical definition and rendered more susceptible to rigorous quantitative research. Moreover, the way is opened to study of these much discussed phenomena (identity development) in many varied groups ranging from ones within our own culture-- ethnically, racially, psychiatrically, socio-economically differentiated--to cross-cultural comparisons.

Proposed Course of the Research. The plan is to complete data collection for a two year period on all of the subjects. This will involve four to five waves of interviews and testing on each subject. The complex data is being currently examined for the most appropriate statistical analysis models. A preliminary outline for the eventual integration of the findings in monograph form, "Lines of Adolescent Development", has been written up. Specific discussions of new methodological and substantive findings during the progress of the studies are planned. The first of these papers,"The Structural Complexity of self-images",is currently being completed.

Honors and Awards:

1. Hauser, Stuart T., Presented "Black and White Adolescent Identity Development" to Adult Psychiatry Branch Seminar, NIMH, September, 1970.

2. Hauser, Stuart T., Presented "Black and White Identity Formation: Aspects and Perspectives" at Fall Meetings, American Psychoanalytic Association, December, 1970.

Publications:

1. Hauser, Stuart T., Black and White Identity Formation, New York, John Wiley and Sons, 1971

2. Hauser, Stuart T., "Black and White Identity Development: Aspects and Perspectives," submitted for publication.

3. Hauser, Stuart, T., and Stobrow, R.D., "A Model For Operationalizing Psychoanalytic Insight," submitted for publication.

Serial No. M-AP(C)-18- 2
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Coordinating "Micro-Codes" in Family Consensual Experience: A Study of the Responses to Speech Hesitancy and Fluency in Family Interaction.

Previous Serial Number: M-AP(C)-18-2

Principal Investigator: David Reiss, M.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.6
Professional:	.1
Other:	.5

Project Description:

Objective: The card-sorting experiment and previous studies by Reiss as well as by Strodtbeck, Mishler, and Waxler, et al., support the notion that families can be distinguished by the shared experience, of their members, of their environment. Furthermore, it appears as if this shared experience serves as a major regulator of moment-by-moment family interaction in a variety of settings. In order to maintain such consensual experience and to utilize it to deal with environment events as they occur on a moment-by-moment basis, family members must be exquisitely sensitive to each other's ideas and feelings at all times. The project was part of a card-sorting experiment in which family members could communicate only by voice; thus each member had to utilize the others' vocalizations to remain continuously integrated in this delicately balanced family process. Recent experimental evidence suggests that family members may utilize changes in each other's patterns of speech hesitancy and fluency for this purpose. We postulated that all families will show significant moment-by-moment response to changes in the fluency patterns of each member. However, some families--which we have termed "environment-sensitive"--are predicted to respond to hesitant speech as a signal pointing to a difficulty or incongruity perceived by the speaker in the laboratory puzzle itself. Other families--we call them

"consensus-sensitive"--will interpret hesitancy as a sign of the speaker's perception of or response to the family itself. These family types are defined by a consensual experience model and identified by their non-verbal performance on a card-sorting procedure. Thus, this study is a further test of the consensual experience model which predicts that family members will respond to minimal changes in each other's speech in ways determined by their over-all shared experience of the environment. These minimal speech changes could then be viewed as a personal, family "micro-code" serving to regulate its interaction in moment-by-moment harmony with its shared experiences and views.

Method: The verbal interaction in the second family problem of the card-sorting task was recorded on a specially prepared 4-channel tape recording system and transcribed by polygraph to give a visual, objective record of patterns of vocalization. A timing signal permitted coordination of the polygraph record with a typescript of the content of the family's discussion. Changes in fluency were measured by methods of Boomer and Dittman, and Goldman-Eisler, using the polygraph record. The family's response to fluency changes in any member was measured using interaction codes developed by Reiss and Mishler and Waxler, using the typescript, and also measures of the card sort and trial times.

Progress: All the polygraph and typescript records have been obtained. The Boomer and Dittman scoring procedures have been successfully adapted for use with the data collected in this study. In addition, the Level of Abstraction Code, from previous work by Reiss, and the Responsiveness Code, from work by Mishler--two coding procedures for measuring verbal interaction--have been adapted for the present project. All three coding procedures are nearly complete. Programming has begun to utilize Attneave's information transmission statistic to analyze relationships among the three codes through time.

Serial No. M-AP(C)-18- 3
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: The Effects of Progressive Isolation of an Individual From His Family on His Perceptual Functioning: Use of a Teletype-LINC Apparatus to Study the Reciprocal Relationship of Family Interaction and Individual Thinking.

Previous Serial Number: M-AP(C)-18-3

Principal Investigator: David Reiss, M.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.4
Professional:	.2
Other:	.2

Project Description:

Objective: Previous experiments in this Section have demonstrated that family interaction does have a specific, predictable short-term effect on the thinking and perception of its members. A critical question is: of all the flux and nuance of family interaction, which aspects are the most critical for regulating the thought and perception of its members. In the card-sorting and micro-code experiments, Dr. Reiss explored the role of various details of the vocalized portion of family interaction--excluding all forms of non-vocal performance. In the current experiment, the question is: to what extent do families differ in the amount of objective information--concerning the problem solution--they can obtain and distribute among its members; and, further, how does this obtained and distributed information regulate perceptual processes in their members. In other words, in what way does an individual's perceptual process--occurring in the midst of a family problem-solving task--depend on the quality and quantity of information provided him about the problem by his family, disregarding all other aspect of the family interaction of which he is a part. It is predicted that families will differ in the amount of relevant information they can discover about the problem, their effectiveness in distributing it to all members of the family and the

use each member makes of information provided to him by others in the family. Specifically, we expect families we have designated as environment-sensitive will extract a great deal of problem-relevant information from their environment, will effectively distribute it amongst members in the family and each member will utilize the information insofar as it assist him in a logical, consistent and comprehensive problem solution. Individuals in families designated as consensus-sensitive will work to obtain, distribute, and utilize problem-relevant information only insofar as it permits a family solution at a desired level of within-member agreement. In the present experiment the procedure progressively isolates each member from his family. In the first condition all information obtained by all members about the problem is transmitted immediately to each individual along with the identity of the family member who obtained it--the "public mode"; in the second condition the information is transmitted after a variable delay without the identity of the member who obtained it--the "anonymous mode"; in the third condition no information is transmitted between members--the only information available to each member is what he obtains himself and that provided by an impersonal, extra-family source--the "standard mode." It is predicted that members in environment-sensitive families will maximally utilize information from any source whereas members in consensus-sensitives will utilize information from their past when it comes from an impersonal source. In order to provide immediate and standardized information transmission between the family members and between the family and the impersonal environment a teletype-LINC apparatus was constructed and programmed. This permitted the conduct of experiments entirely under the control of computer. It further permitted every item of family interaction, i.e. transmission of information by use of teletypes, to be precisely recorded in time. Thus, at the conclusion of the experiment it is possible to know not only what interaction has occurred but precisely when. This will permit an exact correlation of the various events comprising the flux of family interaction in this experimental setting. The teletype-LINC apparatus represents a major innovation in experimental social psychology and this project, in addition to its exploration of a particular hypothesis about family interaction, serves as an initial study of this innovation.

Method: Four family members, the parents and two children, are seated in booths so they cannot see each other. Each has a teletype and is instructed in its use. They are told that they must discover a class of symbol sequences that, when typed, will result in plus (+) being typed in return--automatically. Their understanding is that the plusses are typed in a systematic way and their job is to discover the system or pattern. Each member is given an example (e.g. CSTTTTTTTS which represents the class of "plus sequences" beginning with CS followed by n number of Ts and concluding with an S). Then each member tries out his own sequences in turn. In the "public mode" each sequence is automatically typed, immediately, on the other members' teletypes, with a symbol indicating whose sequences it was and when it received a plus or not. In the "anonymous mode" the sequence is typed, along with its plus or minus, after a variable delay in a way concealing its authorship. In the

"standard mode" the sequence typed by each member is not typed on anyone else's teletype; instead, a sequence from a standard library, stored in the computer, is typed on everyone else's teletype. Each mode is introduced by detailed instructions and considerable practical experience for the family so that they become fully familiar with its distinctive features before beginning the actual problem-solving. Preceding and following each experimental problem each member is given an objective test of his ability to predict the class of sequences that will get a plus; this serves as a test of his ability to recognize relevant patterns.

Progress: In the first study, four families designated as consensus-sensitive were compared with four environment-sensitive families. The distinction between these two groups was made by the use of card-sorting procedure. The consensus-sensitive families were those that sought to achieve consensus at the price of accurate problem solution. The two groups were carefully matched for a number of variables including intelligence and social class. The results were very striking and clear even though, in this pilot study, the sample was small. We used a matched-pair design in which an environment-sensitive family was matched with an consensus-sensitive family. In each pair the consensus-sensitive family showed a progressive improvement in problem-solving ability as intermember access was reduced from the public, to the anonymous to the standard mode. In sharp contrast each environment-sensitive family showed no change or a slight decline in problem-solving ability as intermember access was reduced.

A second study, using a wider sample of 15 families, studied the more detailed processes of hypothesis testing in the two groups of families. Correlational studies suggested that members in families with a marked deficit in the public mode relative to the standard mode, used others' hypotheses as a basis for their own hypothesis testing less often than members in families without such a relative deficit. Moreover, in the public deficit, members were less willing to risk the construction of incorrect hypotheses. These findings were predicted by a consensual experience model: It states that members in environment-sensitive families (with no public deficit) use each others' experiences with the environment as a way of augmenting their own experience and understanding of it, whereas consensus-sensitive families, since they are oriented to achieving an agreed-upon internal version of experience, tend to ignore the others interaction with the environment. The unwillingness of these individuals to risk negative feedback, for their hypotheses, confirms our view that they experience negative feedback as censorious rather than information-giving; this attitude is consistent with their view of the environment as hostile and unknowable.

After completing the two studies described above, the program for the teletype experiment was substantially revised to: (a) make the three modes more nearly identical in the type and quantity of feedback for subjects' hypotheses and (b) to more completely automate the procedure; this now includes some automatic instruction and testing of subjects. Pre-experimental trials,

during the past year, have indicated that the changes have improved the efficiency, standardization and comprehensibility of the procedure.

Honors and Awards:

1. Reiss, D.: Invited address. "Intimacy and Problem Solving: An Automated Procedure for Testing a Theory of Consensual Experience in Families." Faculty of the Neuropsychiatric Institute, UCLA, Los Angeles, California, October, 1970.

Publications:

1. Reiss, D. and Sheriff, W.H., Jr.: A computer-automated procedure for testing some experiences of family membership. Behav. Sci. 15: 431-443, 1970.

2. Reiss, D.: Intimacy and problem solving: An automated procedure for testing a theory of consensual experience in families. Arch. Gen. Psychiat. in press.

3. Reiss, D.: Varieties of consensus experience I. A theory for relating family interaction to individual thinking. Fam. Process. In press.

4. Reiss, D.: Varieties of consensual experience II. Note on dimensions of a family's experience of its environment. Fam. Process. In press.

5. Reiss, D.: Varieties of consensual experience III. Contrast between families of normals, delinquents and schizophrenics. J. Nerv. Ment. Dis. 152: 73-95, 1971.

6. Reiss, D.: Schizophrenia: Current research dilemmas. Professional Psychologist. In press.

7. Reiss, D. and Elstein, A.S.: Perceptual and cognitive resources of family members. Contrasts between families of paranoid and nonparanoid schizophrenic psychiatric patients. Arch. Gen. Psychiat. 24: 121-134, 1971.

Serial No. M-AP(C)-18- 4
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: The Effects of Medication on Family Interaction.

Previous Serial Number: M-AP(C)-18-4

Principal Investigator: David Reiss, M.D.

Other Investigators: None

Cooperating Units: Dr. Carl Salzman, Massachusetts Mental Health Center, Boston, Massachusetts

Man Years:

Total:	1.0
Professional:	.3
Other:	.7

Project Description:

Objective: There are three major objectives to this study. 1) The study of the effect of giving a psychoactive drug to a psychiatric patient on his interaction with his parents and the interaction of the parents with each other. The orienting hypothesis is that a complete understanding of the psychoactive properties of a drug must take into account the interpersonal relationships of the patient to whom it is given. The present investigation was designed to test one aspect of this hypothesis, viz. that a psychoactive drug given to one member of a family threesome will rapidly affect the interaction of all three. If this hypothesis is borne out, a follow-up study will be planned to determine if the long-term psychoactive effect of the drug on the patient depends, to a significant extent, on the nature of this immediate or rapid effect on family interaction. 2) To develop a model for studying the extent to which certain classes of family interaction, often categorized as "pathologic," may be regarded as a response to rather than the cause of psychopathology in the child. In the current experiment we give a psychoactive drug, to psychiatric and normal children, which causes an acute impairment in perceptual and cognitive function. The data are expected to suggest what forms of family interaction can be considered a response to this acute, exogenously-caused perceptual and cognitive disorder in the child. 3) The experiment is considered a further test of a number of corollaries of the model of "consensual experience."

This model has been used to derive the majority of specific predictions of the family's response to medication given to the child. Confirmatory findings can be construed as strengthening the overall model.

Method: The sample consists of 12 psychiatric patients and their parents and twelve normal children and their parents. The children are age 16 or older and have taken no drugs for two weeks prior to the study. The parents are 60 or less. In half of each sample the child is given 175 mgm of Seconal, orally, and in the other half a placebo on a double-blind basis. The drug and placebo group within the normal and psychiatric sample are matched on several variables as described below. The study of each family takes place on two successive evenings. On the first evening, the family is tested using a card-sorting procedure. The child is given neither drug nor placebo and the data from this session is used for matching purposes only. On the second night the child is given a drug or placebo on a double blind basis. The drug assignment procedure permits an almost precise matching of the drug and placebo groups according to their performance in the experiment on the first night. In addition they are matched for intelligence. Thus, the drug and placebo groups are identical, or nearly so, with respect to test performance and intelligence. We assume this means that these families are nearly identical in all attributes that are critical for their performance in the testing situation. Other data have suggested that there is a high degree of intra-family stability of performance in the card-sorting procedure so that we assume that the families' performance on the first night is highly predictive of their performance on the second night in the absence of our major experimental manipulation; the giving of a drug to the child. One hour after the child is given the drug or placebo the family is tested on a similar but not identical card-sorting procedure.

The major analyses were the effect of the drug on: 1) The child's performance when working alone--relatively independent from his family; 2) The problem-solving effectiveness and style of the family group and 3) Family speech patterns (e.g. amount of speech, interruptions, separate statements) which were measured automatically using a polygraphic record of vocalization and a computer analysis.

Progress: The data analysis was completed during the past year. 1) Drug effect on the offspring. Subjectively the fathers and offspring, but not the mothers, were able to distinguish whether a drug or placebo had been given. The offspring felt he was impaired by the drug, particularly in relationship to the rest of the family. Objectively, there was a slight impairment in problem-solving performance in the offspring, particularly in normal families, when the offspring was compared to his parents. 2) Family problem solving. There was a substantial difference between normal and patient families in problem-solving effectiveness and style; these differences precisely replicated those found in our previous studies. There was no effect of the drug here. 3) Speech patterns. Families with drugged offspring talked more and interrupted each other more. Detailed analyses

suggested that these speech patterns were compensatory; they permitted the family to resist the effects of the drug on their typical mode of problem solution. With regard to our three major objectives, the data suggested 1) Acute psychoactive drug administration does not produce fundamental changes on family problem-solving patterns; any changes observed in their interaction may be more superficial and compensatory, allowing them to persist in old patterns in the face of the new challenge provided by the drug effect; 2) The acute psychologic deficit in the child did not alter the more basic patterns of problem solving; indeed the changes that were produced tended to make the patient families interact more like the normals rather than the reverse; 3) Since problem-solving patterns express the family's shared experience of the laboratory, according to our past investigations, we concluded that the drug did not make any basic alteration on these kinds of shared constructions.

Serial No. M-AP(C)-18- 6
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Nurse-Doctor-Patient Interaction: An Experimental Study of Its Role in Patient Acculturation on Psychiatric Wards.

Previous Serial Number: M-AP(C)-18-6

Principal Investigator: David Reiss, M.D.

Other Investigators: None

Cooperating Units: Richard Almond, M.D., Department of Psychiatry, Stanford University Medical School, Palo Alto, California

Man Years:

Total:	.4
Professional:	.1
Other:	.3

Project Description:

Objectives: The major objective of the study is the direct measurement, under controlled conditions, of nurse-doctor-patient interaction as it occurs on psychiatric wards. The hypotheses of the study are derived from previous work by Dr. Almond which suggest that particular forms of nurse-doctor-patient interaction are crucial to inducing change and improvement in patients. Moreover, his previous studies suggest that certain value orientations by the staff serve to control or perpetuate these crucial interactions and many patients, after modifying their behavior during interaction with professional staff (and other patients), accept these values. This study seeks to relate value orientations of the staff, concerning types and process of treatment as well as personal preferences for types of interaction in group involvement, with the way they interact with each other and with patients. Specifically, we attempt to predict how a nurse and doctor will interact with each other from a knowledge of their value orientations; then we seek to predict how the nurse-doctor dyad will interact with a patient, based on their behavior when interacting as a dyad. This is one of the first direct experimental studies of interpersonal processes amongst psychiatric personnel and therefore the project also serves the general purpose of examining the value of experimental techniques in this area of clinical investigation.

Method: Dr. Almond has modified a questionnaire he used in his original studies in New Haven. It has a broader range of items and is now suitable for administration to nurses and doctors as well as patients. The results of this questionnaire were used to evaluate nurses' and doctors' value orientations. These orientations, in turn, were used to predict nurse-doctor interaction. Two value orientations were selected as independent variables. 1) the subjects' expressed valuation of social openness and involvement in the ward (SOWI) by patients and staff; 2) the subjects' expressed wish to be included in and control groups (FIRO). Sixteen nurse-doctor dyads were formed so that they could be divided into four subsamples of equal size; 8 dyads were highly discrepant on SOWI (more higher) and 8 had similar scores; half of each of these subsamples had highly discrepant FIRO scores (more higher) and half were the same. Each dyad was tested separately in a small-group-type laboratory where they were isolated in booths and could communicate only by microphone. They worked on a standard set of problems, provided by the experimenter, requiring them to group a set of fictitious patients into activity groups. After a series of such problems, they were joined by a patient and continued to work on a set of similar problems as a triad. A number of objective indices of social interaction in the dyads and triads were derived from the card placements and objectively recorded times of various phases of the experimental task. These variables sought to measure the extent to which the dyads and triads 1) agreed or disagreed on problem solutions; 2) blindly followed a potent leader or worked interdependently with each individual making a substantial contribution; 3) utilized the full range of ideas elaborated by each person working alone; 4) "objectified or dimensionalized" the problem rather than seeing each fictitious patient and grouping as unique and personal.

Progress: Data analysis is complete and the project is being written up. The basic findings are these: There is a substantial difference in the effects of independent variables early in the task, when the nurse and doctor are being acquainted and where the dyad meets the patients for the first time, and later in the task when all three have been working together. Dyads where the nurse is higher in valuation of ward openness or in group affiliative disposition (FIRO), cannot effectively perceive or structure the problem in the same way. There is evidence of division and estrangement. When the patient joins the dyad the doctor and the nurse try to accomodate themselves to the patient's views but do not achieve any further consensus between themselves. The patient himself shows considerable evidence of feeling very isolated and estranged in the experimental situation and appears to provide an opportunity for a nurse or doctor, who feels the same way, to form an alliance or coalition with him. Later in the task, after the acquaintanceship process among all three has taken place, the evidence shows that discrepancies, in group affiliative dispositions, play less of a role. Instead, nurses who value open and involvement in ward treatment programs, appear to exert a major influence over the dyad no matter what their group affiliative tendancies are. These triads prefer larger activity groups and discuss assignments in more direct and earthy, rather than abstract terms. Indeed, they appear the most comfortable and engrossed in the task of establishing patient groups--a predictable consequence of the nurses enthusiams for group treatment approaches.

Serial No. M-AP(C)-18- 9
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Stability of Family Problem Solving Over Time.

Previous Serial Number: M-AP(C)-18-9

Principal Investigator: David Reiss, M.D.

Other Investigators: Loann Drake

Cooperating Units: None

Man Years:

Total:	.2
Professional:	.1
Other:	.1

Project Description:

Objective: The overall theory of consensual variety, which has generated most of the projects in this Section, stipulates that subjective constructs of families are fairly stable over time. Indeed, a construct is thought to be an enduring feature of the family by which it may be distinguished and typed. The stability of these constructs is now a matter largely of inference. The current study is designed as a first in the series of approaches to directly determine the stability of performance by which the family construct is operationally defined.

Method: A companion to our basic card-sorting procedure was designed. The basic procedure uses cards each containing a patterned sequence of nonsense syllables in the individual tasks and letters in the family task. A new task was developed, using the same kinds of finite state grammars that generated the patterned letters and syllables, using numbers as symbols instead of letters. Pre-experimental tests showed it to be about the same difficulty as letter syllable-sorting task.

Progress: A pilot sample of fifteen families showed that there was substantial stability in measures of problem solving effectiveness, coordination and closure over a period of 24 hours and of approximately a year. A larger and more systematic study is being planned to determine family stability on these and other variables.

Serial No. M-AP(C)-18-10
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: The Effect of Stimulus Materials on Family Problem Solving.

Previous Serial Number: M-AP(C)-18-10

Principal Investigator: David Reiss, M.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.1
Professional:	.1
Other:	.0

Project Description:

Objective: In the work done in our laboratory almost all family problem-solving tasks have utilized pattern recognition tasks in which patterned stimuli have been generated by one or another type of finite state grammar (as originally described by Chomsky and Miller). These problem materials have a number of advantages for studying complex perceptual and cognitive processes. Nonetheless, they represent a restricted model of the types of stimulus experience families may encounter in their everyday lives. It is important to establish that our findings concerning family problem solving can be generalized to different kinds of stimuli. Other features of the card-sorting procedure, such as the partial self-administration features, ease of observer recording of sorting performance, uniformity of physical characteristics of the stimulus materials, isolation in booths, have solved a number of long-standing methodological problems. Thus, it seemed imprudent to change the basic card-sorting procedure itself. However, a change of the content of the cards seemed useful to test the generality of our findings.

Method: Accordingly, we designed a procedure, adapted from Tien's Organic Integrity Test, which required subjects to sort cards according to objects pictured on the cards. Three sets of 15 cards were developed: two were used for initial and final individual task and a third for a family

task between the individual tasks. Thus, the procedure has the same formal structure as the letter syllable and number-sorting tasks. In each of three tasks the cards can be grouped in at least three ways: by color of object, use of object (e.g. tool, wearing apparel or sporting equipment) or by sex of user (male, female or neutral). A maximally effective sort would presumably use one of these three with complete consistency (corresponding to recognizing the finite state grammar in the basic sorting procedure). Also, families could vary in the amount of sorting similarity between members and across trials. Therefore, the same variables of problem-solving ability, coordination and closure were obtainable from this procedure as the basic procedure.

Progress: Data collection is continuing.

Serial No. M-AP(C)-18-11
1. Adult Psychiatry Branch
2. Section on Experimental Group and Family Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Eye-Movement Studies of Size-Estimation

Previous Serial Number: M-AP(C)-18-11

Principal Investigator: Richard Stillman, M.D.

Other Investigators: David Reiss, M.D.; Dolph Pfefferbaum, M.D. and Monte Buchsbaum, M.D.

Cooperating Units: None

Man Years:

Total:	1.2
Professional:	1.0
Other:	.2

Project Description:

Objective: Eye-movements mirror critical information-processing decisions of the subject, including decisions about what is important, what has been sufficiently assimilated, what needs to be looked at or looked for next, and how broadly or intensively the visual world needs to be scanned. Previous studies have established considerable construct validity for eye movement recordings in various situations ranging from chess problem solving to the TAT. Recording eye movements permits microscopic observations and analyses of an extremely complex and fundamental kind of behavior. These movements occur so rapidly that they are usually only partially under conscious control and so provide information which might be lost in a task where a subject feels the need to create a certain appearance. In addition the movements themselves can serve to trigger new stimuli if a responsive element is introduced into the experiment, such as a small computer.

We are interested in the careful and explicit description of individual differences in perceptual and problem-solving strategies, including differences between normals and patients, and differences over time in patients with fluctuating illness.

Method: All the experiments planned involve a loop including the subject, who can respond with eye movements and with a number of finger switches, a Mackworth corneal-reflection camera with a red marker light, a video camera (with monitor) inputting an analog circuit which emits the X-Y coordinates of the eye spot seen by the TV camera to the LINC computer which records these coordinates and can decide whether to maintain or change the display shown on the cathode tube facing the subject. A separate program enables the computer to present, in summary or extended form, a visual "replay" of the preceding testing bloc, showing superimposed the eye movements and the stimuli presented. The stimuli being used currently are two squares, the task being to decide whether one is larger than the other.

Progress: The equipment has been assembled and several programs for the LINC computer have been written. Over a dozen normal subjects have been tested and the data has been analyzed to reveal highly reliable individual differences in such parameters as rate of fixations, direction of initial fixation, and response time. These findings complement others which are just now appearing in the literature and have considerable importance as a base-line for future research.

Serial No. M-AP(C) 19-1
1. Adult Psychiatry Branch
2. Section on Twin & Sibling Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Progress Report
July 1, 1970 through June 30, 1971

Project Title: Comparative Studies of Discordant Siblings in Families of Schizophrenic, Juvenile Delinquent and Well-adjusted Young Adults

Previous Serial Number: same

Principal Investigator: William Pollin, M.D.

Other Investigator: Martha Werner, M.A.

Cooperating Units:

University of California-Davis, Dr. Joe P. Tupin
University of Connecticut, Dr. James R. Stabenau

Man Years (Computed for the 12 month period)

Total:	1.0
Professional:	.6
Other:	.4

Project Description:

Objectives, Methods Employed, Patient Material, and Major Findings of this study have been extensively described in previous years' reports. At present, activities are limited to completion of ten-year followup home visits, and integration and preparation of the data for monograph publication.

Significance to Mental Health Research: This project, along with the other ongoing studies in schizophrenia concurrently under way in the Section, are all addressed to the two major goals of helping to define etiologic factors relevant to schizophrenia, and more basically, determinants of personality formation. As such, they are relevant to major ongoing questions of the determinants of mental health and emotional illness.

Proposed Course of Project: Integration of sibling data with that from twin studies (19-2 and 19-5 below) for monograph publication.

Honors and Awards; Publications:

None

Serial No. M-AP(C) 19-2
1. Adult Psychiatry Branch
2. Section on Twin & Sibling Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies in the Development of Personality and Psychopathology in Identical Twins Discordant for Schizophrenia

Previous Serial Number: same

Principal Investigator: William Pollin, M.D.

Other Investigators: none

Cooperating Units:

A. NIMH:
Social Service Department, (Barbara Scupi)
Laboratory of Psychology, Office of the Chief
Adult Psychiatry Branch, Office of the Chief, (Drs. Lyman Wynne and Margaret Singer)
Laboratory of Clinical Science (Dr. Irwin J. Kopin)
Office of Biometry (Karen Pettigrew)
Computer Systems Branch, Office of Administrative Management (Nils Mattsson)
Center for Studies of Schizophrenia, CRB, ERPC (Dr. Loren Mosher)
B. University of California-Davis (Dr. Joe P. Tupin)
University of Connecticut (Dr. James R. Stabenau)

Man-Years (computed for the 12 month period):

Total:	.9
Professional:	.4
Other:	.5

Project Description:

Objectives: In identical twins discordant for schizophrenia, genetic, racial, ethnic, social class and a variety of other variables which have seemed to bear some relationship to the pathogenesis of this illness are constant for both twins. Therefore, in studying pairs in which one twin is schizophrenic and the other is not, there exists an unusually favorable situation within which to attempt to determine what life history events, family relationship patterns and non-genetic biologic factors play a role in the etiology of this illness, and in what manner. This is our objective.

Methods Employed: Previous reports have described the intensive multidisciplinary inpatient work-up of a total of 25 families with identical twins admitted for evaluation to the Clinical Center. During the past year, computer analysis of multidisciplinary quantitative variables has continued, along with planning for replication studies (see 19-5, below). However, progress has been slowed by staff changes and other problems. Dr. Mosher has also re-analyzed data for pregnancy and birth complications and their relationship to schizophrenia.

Patient Material: See previous reports for details. Fifteen monozygotic twin pairs discordant for schizophrenia and their families (one pair became concordant); ten control twin families.

Major Findings: Previous reports have described earlier findings. Differences distinguishing index schizophrenic from non-schizophrenic co-twin controls in discordant pairs have included family perception and relationship differences, life history and non-genetic constitutional differences.

Last year we reported preliminary evidence that some abnormality of catecholamine metabolism might be related to genetic predisposition to schizophrenia. This was based on the observation that in the discordant pairs most catecholamines and their metabolites were equally elevated in the index schizophrenic twins and their non-schizophrenic co-twin controls, independently of the presence or absence of psychosis. There was a highly significant interclass correlation coefficient for the catecholamines, which strongly suggested a high degree of genetic control. Conversely, 17-hydroxy steroids showed an elevation only in the index schizophrenic twin, and the non-schizophrenic co-twin controls showed the same mean and range of values as the normal twins who had never had any significant psychopathology. However, we have since found that MHPG, the metabolite believed to most accurately reflect CNS catecholamines, is the one catecholamine metabolite measured which does not show this pattern. It is neither elevated in the schizophrenic group, nor is there a high intraclass correlation coefficient. This finding fails to substantiate the hypothesis that previously described elevation of catecholamines could reflect a disturbance of CNS neurotransmitter, the most parsimonious explanation. The finding, nevertheless, requires further exploration.

Significance to Mental Health Research: Previous analysis had focused on the significance of defining a) non-genetic constitutional contributions toward the pathogenesis of schizophrenia, and b) a characteristic pre-illness life course preceding schizophrenia. The findings of the past two years may point to some of the genetically determined biological factors which contribute to predisposition to this psychosis.

Proposed Course of Project: Continuing analysis of multidisciplinary data with further efforts to trace central relationships involved. Replication study as described below (19-5).

Honors and Awards:

Pollin, William: Guest lecturer, "A Genetically Controlled Biological Substrate of Schizophrenia and Other Psychoses," World Psychiatric Association, USSR Academy of Medical Sciences Symposium on Schizophrenia, Leningrad, USSR, September 27, 1970.

Pollin, William: Guest lecturer, "A Genetically Controlled Biological Substrate of Schizophrenia and Other Psychoses," Psychiatric Research Society Meeting, San Diego, California, February 14, 1971.

Pollin, William: Guest lecturer, "A Possible Genetic Factor Related to Psychosis," Annual Meeting of American Psychiatric Association, Washington, D. C., May 7, 1971.

Publications:

Mosher, L., Pollin, W., and Stabenau, J.R.: Identical twins discordant for schizophrenia: neurological findings. (Accepted for publication Arch. Gen. Psychiat.)

Serial No. M-AP(C) 19-5
1. Adult Psychiatry Branch
2. Section on Twin & Sibling Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Distribution and Concomitants of Schizophrenia, and Other Psychopathologies, in a Systematic Sample of 15,909 Twin Pairs

Previous Serial Number: Same

Principal Investigator: William Pollin, M.D.

Other Investigator: Stephen Cohen, M.D.

Cooperating Units:

A. NIMH:
Laboratory of Clinical Science, Section on Psychiatry (Dr. William Bunney)

B. National Academy of Sciences/National Research Council (Dr. Z. Hrubec)
Georgetown University (Dr. Martin Allen)

Man Years (Computed for the 12 month period)

Total:	2.3
Professional:	1.5
Other:	.8

Project Description:

Objectives:
1. To determine which of the differentiating factors previously uncovered in our study of a series of identical twins discordant for schizophrenia can be validated by analyzing a much larger systematic series of twins discordant for schizophrenia.

2. To determine which, if any, of these factors are specifically relevant to schizophrenia, and which instead may predispose toward non-schizophrenic psychosis, or non-psychotic psychopathology.

3. To evaluate the relative genetic component in the etiology of schizophrenia, in comparison to other psychopathologies.

Methods Employed:
In a National Research Council sample of 15,909 pairs of male twins, both of whom served in the Armed Forces, and for whom extensive medical follow-up

common clinical yardstick has been applied to all subjects reviewed, and obvious errors located and corrected. In the 840 charts reviewed during this year there were 268 charts where changes in zygosity, diagnosis, or disease course were made.

3. Current revised data show the following: (Some of these figures are subject to slight further modification.) For schizophrenia, 26 of 95 MZ pairs (27.4%) and 6 of 125 DZ pairs (5.7%) were concordant. The MZ/DZ ratio is 5.7 and H = .373.

In contrast, for affective psychoses 5 of 13 MZ pairs (38.5%) and 0 of 27 DZ pairs (0%) were concordant. To make possible computation of an MZ/DZ ratio, we assume the next DZ pair would be concordant, the MZ/DZ ratio then becomes 10.8, and H = >.556.

If we separate out schizo-affective diagnoses, they show a pattern more similar to affective than to schizophrenic psychoses with respect to these distribution variables. Seven of 14 MZ pairs are concordant (50%), 0 of 12 DZ pairs are concordant (0%), the MZ/DZ ratio is infinite, (or at least greater than 6.5) and H = >0.612.

4. The chart review has also yielded specific long-term (20 years) information concerning course of psychotic illness, certain psychodynamic variables, concurrent medical illnesses and mortality data that will aid in obtaining a reliable sample for more intensive study.

Significance to Mental Health Research:

1. The revised findings help document the conclusion that there is a significantly greater genetic factor contributing to the pathogenesis of affective as compared to schizophrenic psychosis. They also indicate that the genetic mechanisms contributing to schizo-affective schizophrenia overlap with, or include, those of affective as well as schizophrenic psychosis.

2. The identification of the above-described groups of MZ twins discordant for different psychopathologies provide large populations admirably suited for testing several major related hypotheses concerning schizophrenia. We have previously described a constellation of familial, life history, and biological factors, derived from intramural studies and the world literature, which has differentiated identical twins who become schizophrenic from their co-twins who do not. Comparison of the sample of MZ pairs discordant for several of the other psychopathologies, will make it possible a) to clarify and integrate into a conceptual scheme those differentiating features which we replicate; and b) to determine which, if any, sub-group of these differentiating factors may be specific for schizophrenia, and which, on the other hand, are related to psychopathology in general. Wynne has pointed out that only a relatively small proportion of persons with possible genetic endowment for schizophrenia actually becomes symptomatically ill; he has proposed certain definable psychophysiologic response dispositions that may characterize potential schizophrenics and has suggested that investigation of

is available, all subjects were located who were computerized as showing any psychiatric diagnosis, or were separated from the Service in such a manner as to indicate disabling psychopathology. Following analysis of the computer data, individual charts of the first subgroup of patients, comprising 420 pairs with one or both diagnosed Schizophrenic Reaction, Involutional Psychotic Reaction, Affective Reaction, and Other Psychotic Reactions were called in from various parts of the country and thoroughly reviewed by a team of three psychiatrists. Those charts that fulfill certain rigid diagnostic criteria for Schizophrenia and Manic Depressive psychosis have been identified and form the nuclear sample for further study.

Planning is under way for subsequent direct contact (via questionnaire, home visit, and/or brief inpatient evaluation) of selected sub-samples drawn from various psychopathology categories. Questionnaires are being prepared for the next stage of contact with the first sub-group of approximately 330 pairs with schizophrenia diagnosis.

Patient Material:

Working with data obtained from 42 states' vital statistic offices, the NAS/NRC located 54,000 pairs of male twins, born between the years 1917 and 1927. Of these, 15,909 pairs were identified by the Veterans Administration as both having served in the Armed Services. These twins represent a cohort born in the decade 1917-1927, and now range in age from 44 through 54; thus the age of maximal risk for the development of schizophrenia has been passed. Zygosity information based on finger prints and/or anthropometric data is available for approximately two-thirds of this sample. Additional data available include complete diagnostic records from Army and V.A. data for all pairs and questionnaire response data for approximately one-half of the sample. Initial analysis was done on computer summaries of this data; this past year's work has focused on chart analysis.

We are currently working with the 420 pairs of the 15,909 pairs for whom data are available, in which one or both twins have been listed as showing the diagnosis of Schizophrenia, Involutional Psychotic Reaction, Affective Reactions, and Other Psychotic Reactions. We will subsequently similarly review the charts of twins with diagnosis for psychoneurosis and a group still to be selected to serve as normal controls.

Major Findings:

1. From the NAS computer tape, 5,256 psychopathology diagnoses were initially identified in 3,614 individuals. These included the following sub-groups of monozygotic, discordant pairs: 401 pairs discordant for psychoneurosis, 112 personality disorders, 166 for psychophysiologic disorders, 23 affective disorders, and 354 pairs discordant for other psychopathology, in addition to the previously described 69 MZ pairs discordant for schizophrenia.

2. Subsequent intensive chart review by a team of three psychiatrists has significantly refined these initial findings. For the first time, a

the inheritance of these response dispositions may be considerably more productive than studies focused on the inheritance of diagnostic entities. The large number of monozygotic twin pairs in the NRC sample discordant for different psychopathologies provide an optimal population for the application of Wynne's proposal, by comparing the non-diagnosed co-twins in the pairs discordant for schizophrenia with the non-diagnosed co-twins of the pairs discordant for neurosis and other non-psychotic psychopathologies; and other approximately selected sub-groups.

Proposed Course of Project:

1. Completion of full analysis of chart review.

2. Questionnaire evaluation of selected sub-samples of the above-described MZ pairs discordant for different definable psychopathologies.

3. Direct study of appropriately selected sub-samples to test the above-described hypotheses.

Honors and Awards:

Pollin, William: Guest lecturer, "The Interaction of Genetics and Environment in the Pathogenesis of Schizophrenia," University of Maryland School of Medicine, Baltimore, Md., December 12, 1970.

Cohen, Stephen, Allen, Martin, Pollin, William and Hrubec, Zdenek: "Schizophrenia in Veteran Twins: A Follow-up Report." Paper presented at Annual Meeting of the American Psychiatric Association, Washington, D.C., May 4, 1971

Serial No. M-AP(C) 19-6
1. Adult Psychiatry Branch
2. Section on Twin & Sibling Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Twin Intrapair-Comparative Technique in the Study of the Determinants of Early Personality Development.

Previous Serial Number: same

Principal Investigators: Donald J. Cohen, M.D. and William Pollin, M.D.

Cooperating Units:
Child Research Branch, NIMH (Nursery School), Dr. Charles Halverson and Gail Inoff (M-CR-24 (C))
Georgetown University, Washington, D. C., Dr. Martin Allen
Children's Hospital, Washington, D. C., Drs. Beale Ong, Jerome Haller and Ann Lodge
Human Genetics Branch, NIDR, Mr. Webster Leyshon
Department of Pathology, NIH, Dr. Louis Thomas

Man Years (computed for the 12 month period)

Total:	1.9
Professional:	1.5
Other:	.4

Project Description:

Objectives:

1. To develop methodologies for the study of the formation of personality in pre-school children, based on the comparative study of pairs of twins. To study differences between children, in relation to a) non-genetic biological differences between the twins; b) parental personality and behavior; c) differences in the congenital endowment of children, with particular reference to the modulation of stimulation; and d) different experiences, such as illness or surgery, and the differential effect on children.

2. To study the developmental roots of personality and family characteristics which have been related in our other studies on schizophrenia to the origins of psychopathology in one twin of an identical twin pair discordant for schizophrenia.

3. To study the early life experiences and differential determinants of personality in twin pairs discordant for physical handicaps, for example, identical twin pairs discordant for cleft lip and palate.

4. To develop methodologies for the study of the physiological and psychological processes related to attention and fearfulness, using identical and fraternal twins.

Methods Employed: Local obstetricians, officers of Mothers of Twins Clubs, and other mothers familiar with our program, refer families to the research program at various times during the gestation of the twins or soon after birth. Preferably, the families are seen while the twins are still unborn. However, for the study of children discordant for physical anomalies, the families are being seen at any point in infancy when the referral is made. The study of the twins includes the following procedures: Developmental evaluation and Bayley testing, neurological evaluation; psychiatric diagnostic evaluations of the twin and parents; family records; information from the Experimental Nursery School of the National Institute of Mental Health in which the children are enrolled at age 2-1/2 for one day or four week studies; evoked cortical potentials; and study of autonomic nervous system changes in different states of attention and emotionality; projective psychological testing at age 3; and social worker family evaluations. Special forms have been developed for developmental history taking, family histories, Rorschach test behavior rating, and ratings of children in experimental situations.

Patient Material: Several different cohorts are being employed in the various studies. The study of the longitudinal development of twins, focusing on identical twins, has a cohort of ten sets of twins ranging in age from two to four years. Four sets of twins are currently in the cohort of vulnerable or potentially vulnerable children studied. This cohort is to be increased. The third cohort has been used for studies of physiological differences in relation to attention, and differences in fearfulness. The pool consists of approximately thirty sets of twins and fifteen sets of triplets. Of these, about seven sets have been studied to date, and the others are scheduled for observation and study over the next month.

Major Findings:

(A) Longitudinal study:

Five sets of twins followed from the time of the diagnosis of twinning in pregnancy through age 3-4, as part of the first cohort of 10 sets of twins, have been in the Child Research Branch, NIMH, nursery school. They have also had projective testing (Rorschach), developmental testing (Bayley), neurological evaluation, and child psychiatric evaluation. Two of these five sets are dizygotic.

Congenital endowment and early competence. The physiological endowment, early adaptation, and overall competence during the first week of life were scored by a new technique, First-Week Evaluation Scale (FWS), which rates each of the following variables from 1 (worst, requires specific attention) to 5 (best, normal); Health; Physiological adaptation; Calmness; Vigor; Attention; and Neurological examination. The ten children were divided into three classes on the basis of these FWS: High FWS; middle FWS; and Low Group. The High

FWS group, contrasted with the low FWS group, contained significantly more girls, firstborn twins, heavier twins, and children of vertex delivery.

Nursery school behavior: The nursery school staff and observers had no previous information about the children. In the nursery school, the child with the high FWS coped well, talked well, and was curious and exploratory. His play was original and highly structured, involving home-situation themes and other sequential activities, in which he was highly involved, and yet he was able to take the leads suggested by the adult (tractable). The low FWS child was markedly more fearful and less talkative. His play was less organized, gross, rough, and flitting. His behavior was more frenetic, he did not achieve the ends he wanted, and he showed difficulty in delaying his behavior to achieve an end.

Rorschach behavior: The Rorschach test was administered to each of the children at about age 3, by an experienced tester with no previous knowledge about the children. The examiner completed a rating scale on the children's general behavior during the testing. The Rorschach behavior was consistent with the nursery behavior: the High FWS group was more competent, talked better, and was more motivated; the Low FWS group was more fearful and showed more difficulty in the control of behavior.

Developmental testing, psychiatric evaluation: The Bayley developmental quotients for the High FWS children were within the top half for all of the cohort, the Low FWS group scores were in the lower half. Psychiatric evaluation revealed that 3 out of 3 of the Low FWS group had significant speech difficulties, including stuttering, baby talk, and lisping. All three High FWS children had unusually well developed language skills, without any articulation problem. Two out of three of the Low FWS group were remarkably immature youngsters, one being quite frightened and the other unusually silly and infantile. . All three of the High FWS children were mature, outgoing, and imaginative youngsters who were independent, well-organized, and yet not obsessively constricted.

Developmental course: The longitudinal, in-depth study of the children and families, the results of the FWS, nursery school, Rorschach testing, developmental assessment, neurological evaluation, and psychiatric evaluation are all consistent with the interactional view of child development, in which the course of development is seen to be the result of a variety of determinants, including innate (genetic, uterine, perinatal) and experiential factors. The psychodynamic study of the families has revealed the importance of early neurological and physiological competence in shaping the child's pattern of responding to the environment and to internal stimulation. Similarly, the data indicate the importance of the family's response to the child's needs and to ways in which parents can shape the behavior of their children.

(B) Vulnerable children:

The study of vulnerable children is still in the start-up stage. Two phenomena are of special interest. First, we have observed the difficulties

experienced by families in forming positive relationships with the twin with the physical anomaly or, where twins are afflicted, with the twin who is more afflicted. Secondly, it has appeared that the involvement of the family with the child before and after a surgerical experience, as seen in one child who had a colostomy and another child who had repair of a cleft lip, can result in an increase in the socialization of the child and of the attachment between the parents and the child. This increased social responsiveness has been observed, as well, in the longitudinal study.

(C) Psychophysiological studies.

The study of twins and triplets in relation to their differential response to new situations, general fearfulness, and processes of attention, is also still in the developmental stage. Methodologically, we have demonstrated the feasibility of constant physiological monitoring of both twins and triplets during psychiatric interviewing, of one hour duration. We have evolved methodologies for studying skin temperature and cardiovascular changes in these toddlers, which we will explore in relation to the results of the psychiatric interviews, maternal descriptions, and the ratings by a psychologist observer, and developmental history. To date, we have been impressed by the differences within the twins and triplet set in relation both to the reported fearfulness by the parents and our observations during the psychiatric interviewing.

Proposed Course of Project: The project will continue to study longitudinally the development of pre-school children using the twin method. In addition, vulnerable children will be studied to highlight variables related to the development of personality. Finally, an intensive study of the physiological and psychological processes related to the major variables uncovered by the longitudinal study will be undertaken. In particular, we are concerned about studying early sensitivity, response to stress, and other related phenomena, to more fully describe differences between twins in relation to their modulation of stimulation, the individual stimulus barriers, and the origins of fearfulness and anxiety. At the present, we are planning to concentrate on behavior observations and cardiovascular autonomic responses as an indicator of some of these processes during early childhood.

Significance to Mental Health Research: We have already had the opportunity, in the longitudinal study, to observe the development of different character patterns. In at least one of the ten children above age 2-1/2, studied in the nursery school, there is indication of significant developmental difficulty. The twin method offers significant advantages in analyzing the contributions of genetic, non-genetic but congenital, and early experiential variables. This will be of particular importance in understanding two areas of critical significance for mental health research: vulnerability to developmental disturbance and the developmental course of disturbance in attention and impulse control. We see our work on attention and fearfulness as central to understanding the roots of several diverse clinical problems, including learning disorders, impulse control disorders, and characteriological

disturbance. Finally, for reasons noted above in relation to the early experiences of all the twins, there is some evidence to indicate that twins as a group constitute a vulnerable population. If so, the intensive study of early lives of twins in general may add to our understanding of the likelihood for the development of significant emotional pathology.

Honors and Awards:

Cohen, Donald J., Allen, Martin G., Pollin, William, Inoff, Gail: "Personality development in ten infant twin pairs." Paper presented at the Annual Meeting of the American Psychiatric Association, Washington, D.C., May 4, 1971

Publications:

Allen, M., Pollin, W. and Hoffer, A.: Parental, birth and infancy factors in infant twin development. (Accepted for publication, Arch. Gen. Psychiat.)

Serial Number: M-AP(C)-20-1
1. Adult Psychiatry Branch
2. Section on Clinical Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Recognizing and Interpreting: A Differentiation of Perceptual and Cognitive Patterns

Previous Serial Number: None

Principle Investigator(s): Lyman Wynne, M.D., Ph.D., Winfield H. Scott, Ph.D.
Hanna Ulatowska, Ph.D.

Other Investigators: None

Cooperating Units: Division of Computer Research and Technology

Man Years (1970-71)
Total: .8
Professional: .7
Other: .1

Project Description:

Objectives: The purpose of the research is to differentiate and study two different approaches to Rorschach responding which have been identified. The first, the "Recognitory" approach, is one in which subjects tend to respond to qualities of the blots with associations to things previously seen. In the other approach, called the "Interpretive" approach, subjects attribute qualities to the blots which are not innate in them, qualities such as movement and depth, and these become important determinants of responses, along with innate qualities. Both approaches can be observed among normal subjects as well as psychiatric patients. The objectives of the research are to do further work in defining and differentiating the approaches, to study both normal and pathological variations on them, and to study their relationships to performances on laboratory measures of sensation, perception and cognition.

Methods: In earlier work on the project, a scoring system was developed to apply to Rorschach protocols to differentiate the approaches to development of responses. The scoring systems have now been applied to protocols of a group of normal college students, and are being applied to those of a variety of psychiatric patients and members of their families. At the same time, extensive clinical data is available on the psychiatric patients and their families, and laboratory data on them and on normal subjects. Using these data, the scoring systems are now being refined, and associations between the approaches to Rorschach responding and clinical observations

on one hand and laboratory observations on the other are being assessed.

Major Findings: A blind evaluation of Rorschach protocols of a group of twenty normal subjects has been completed. Application of the scoring system to these protocols reveals that the system does differentiate the two approaches in this group of subjects. There is evidence to suggest that it will differentiate groups of psychiatric patients. For example, while unipolar depressed patients demonstrate an Interpretive style, bipolar patients, both depressed and manic demonstrate a flat Recognitory style. Certain groups of schizophrenic patients may also be differentiable on the basis of their Recognitory and Interpretive styles.

Significance to Mental Health Research: The research may allow development of new systems of classifying patients in terms of diagnostic, therapeutic and prognostic variables which are associated with fundamental aspects of psychophysiological functioning.

Proposed Course of the Project: It is proposed to apply the scoring systems to the study of Rorschach productions of a range of normal and psychiatric subjects to further study the relationship between the Interpretive and the Recognitory approaches and symptomatology, premorbid adjustment, success of treatment, prognosis and general characteristics of perception and thinking.

Serial Number: M-AP(C)-20-2
1. Adult Psychiatry Branch
2. Section on Clinical Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychological Studies of Character Development in Adolescence

Previous Serial Number: M-AP-(C)-20-2

Principle Investigators: Winfield H. Scott, Ph.D., Roger L. Shapiro, M.D.

Cooperating Units: Section on Personality Development

Man Years: (1970-71)
Total: .05
Professional: .05
Other: 0

Project Description:

Objectives: The general purpose of the project is to study influences on character development among a group of well functioning normal adolescents in contrast to others who present acting out as a major psychiatric symptom. The former group consist of students at a private high school, who are psychologically tested, observed in interaction with their families, and observed in a group situation in relation to their peers. The acting out adolescents are selected from among patients admitted to the 3-West unit. The primary focus in the research is on the relationship between parent-child interactions on one hand, and child-peer interactions on the other, as these differ from one group to the other.

Methods: The main data for the study are psychological test materials, particularly projective techniques, on normal adolescents, acting out adolescents, and on parents of both groups.

Significance to Mental Health Research: The project represents an effort to develop a theory about the genesis of a common psychiatric symptom.

Proposed Course of the Project: Writing is now in progress and the project will be closed upon its completion.

Honors and Awards: None

Publications: None

Serial Number: M-AP(C)-20-4
1. Adult Psychiatry Branch
2. Section on Clinical Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Consensus Rorschach and Focused Feedback as a Clinical Procedure

Previous Serial Number: None

Principle Investigator(s): Winfield H. Scott, Ph.D., Elizabeth B. Sherwood, M.A., Carol A. Langsner

Other Investigators: None

Cooperating Units: Section on Personality Development, Section on Family Studies

Man Years (1970-71)
Total: 1.00
Professional: .8
Other: .2

Project Description:

Objectives: The purpose of the research is to explore the use of the Consensus Rorschach and focused feedback as a clinical technique. The Consensus procedure was originated by Drs. Nathene Loveland, Lyman Wynne and Margaret Singer. While consensus procedures have previously been employed in the experimental study of families of schizophrenics and others, the current work involves exploration of the potential applications of this procedure to clinical assessment. The family is now part of the diagnostic team in that they are asked to review their own performance during "focused feedback" sessions. In these sessions psychologists lead the family members in a discussion of their performance through the use of videotape or audiotape replay of the Consensus Rorschach. A major objective of the research is to examine the effectiveness of the feedback procedure in changing the performance of family members in a subsequent Consensus Rorschach. A second goal is to determine which (if any) type of feedback has greatest effects on self image.

Methods: Each family assigned to 3-West is asked to participate in the project. Both parents, the index, and one sibling closest in age to the patient take part in the Consensus Rorschach. They are required to see how many agreements they can reach about what an inkblot looks like;

following that they each work individually to indicate on a photograph of the blot what agreements have been reached. The inkblots used are both Rorschach blots and a special series made particularly for this purpose by Mrs. Carol Langsner. This session is videotaped and audiotaped. Each family is then randomly assigned to one of the following four procedures: videotape replay with examiners (two psychologists), videotape replay with no examiner, audiotape replay with examiners, and no feedback. During video and audio tape sessions where the examiners are present the family members are instructed to examine their behavior looking for patterns of interaction. The final procedure occurs when the family retakes the Consensus Rorschach. The development of a system of scoring the Consensus Rorschach is underway. Comparisons can then be made between families and before and after feedback sessions.

Major Findings: None to date.

Significance to Mental Health Research: The project may result in a technique useful to apply as a part of clinical evaluation of families prior to their beginning in family therapy. It is likely that performance in the consensus procedure and feedback sessions will have prognostic value, revealing something about the capacity of the family to engage in process of regarding themselves as a group which has effects on its individual members.

Honors and Awards: None

Publications: None

Serial Number: M-AP(C)-20-5
1. Adult Psychiatry Branch
2. Section on Clinical Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychological Studies of Patients with Affective Disorders

Previous Serial Number: None

Principle Investigator (s): Winfield H. Scott, Ph.D., Edward F. Donnelly, Ph.D.

Other Investigator(s): Dennis L. Murphy, M.D.

Cooperating Units: The Laboratory of Clinical Science, Section on Psychiatry

Man Years: (1970-71)
Total: .45
Professional: .4
Other: .05

Project Description:

Objectives: The purpose of the research is to study differences in psychological test response patterns between patients with affective disturbances and other psychiatric patients, and to study the relationship between test response patterns and a range of clinical and experimental variables among patients with affective disturbances. Efforts will be made to relate test performance patterns to such clinical variables as premorbid functioning, course of illness and post-morbid adjustment.

Methods: Studies are now in progress of the test response patterns of patients with a variety of affective disturbances. Subjects include unipolar depressed patients, bipolar depressed and manic patients. A large variety of data exist on affectively disturbed patients who have, in the past, been admitted to the Clinical Center for evaluation and treatment. Their records include psychological test data, and extensive clinical and laboratory data as well. Patterns of psychological test data are now being studied in relation to aspects of premorbid adjustment, course of illness during hospitalization, and adjustment following hospitalization. During the current phase of the research, special attention is being paid to the relationship between patterns of test response and uni- versus bi-polar depressions. In addition, the relationship between test patterns and laboratory data may be studied.

Major Findings: There are reliable differences in the test response patterns of patients with unipolar depressions on one hand, and bipolar patients -- whether depressed or manic -- on the other. For example, on the Rorschach, patients with unipolar depressions develop responses which are dynamically expressive communications of feelings and perceptions while bipolar patients develop responses which are concretely related to the inkblots. Such differences permit a classification of patients from test performances which corresponds directly to classification of the same patients from clinical and laboratory data.

Significance to Mental Health Research: The research may result in a refined classification of patients with affective disturbances related to psychological test performances, patterns of perceptual and cognitive functioning, aspects of premorbid functioning and postmorbid adjustment.

Proposed Course of the Project: It is proposed to develop the observations about differentiating features in psychological tests further, and to study these features in relation to other data on patients who have been admitted to the Clinical Center for treatment and study.

Serial Number: M-AP(C)-20-6
1. Adult Psychiatry Branch
2. Section on Clinical Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychological Assessment of Deficits in Affective Psychosis, Epilepsy and Schizophrenia

Previous Serial Number: None

Principle Investigator(s): Edward F. Donnelly, Ph.D., James K. Dent, Ph.D.

Other Investigators: Dennis L. Murphy, M.D., Thomas N. Chase, M.D. and Carol A. Langsner

Cooperating Units: Laboratory of Clinical Science, NIMH and Surgical Neurology Branch, NINDS

Man Years: (1970-71)
Total: .40
Professional: .30
Other: .10

Project Description:

Objectives: To study patterns of deficit in personality, intellectual, cognitive and perceptual functioning in relation to forms of psychopathology and drug-induced changes in psychopathology.

Methods: Patients with such contrasting disorders as unipolar and bipolar depressions, psychomotor and other forms of epilepsy and varieties of schizophrenia are studied with psychological measures of intellectual, personality and CNS functioning. These include the Halstead-Reitan Battery, MMPI and WAIS. Measures of psychopathology include the Bunney-Hamburg Scale (affective disorders only), patient status on the unit, diagnosis, months of hospitalization and so forth.

Major Findings: On the MMPI, there is evidence of a greater degree of psychiatric disturbance among epileptic patients than among college students. But test evidence would not support the widely-held impression, derived from clinical observation, that psychomotor epileptics show greater disturbance than other epileptics. Although the use of the Halstead-Reitan test battery in differentiating between patients with and without brain damage has been successfully demonstrated, the more schizophrenic patients included in the group without brain damage the less discriminant the battery becomes. When patients with temporal lobe epilepsy were compared to a group of patients with affective

disorders on the same test battery, the results are essentially the same - a lowering of discriminant validity - as those obtained with schizophrenics. It appears that the inclusion of severe psychological disorders in comparison groups tends to lower the otherwise high differentiating function of the test battery. The results of this investigation suggest that a possible explanation of the apparent similarity on the test battery between brain-damaged groups and those with schizophrenia and affective disorders might be a degree of cerebral dysfunction common to all three groups. Alternatively, deficiencies in functioning may be due to factors other than CNS impairment such as inattentiveness or low motivation to perform well.

Significance to Mental Health Research: Deficits appear in measures of intellectual, personality and central nervous system functioning among patients with known organic impairment, and also among psychiatric patients without known organic impairment. The patterns of impairment may differ from one group of patients to another. Clarification of these patterns would increase the usefulness of psychological tests in differentiating cases diagnostically, and, additionally, it may shed light on the nature of central nervous system impairment for various disorders.

Proposed Course of Project: In addition to the psychological and neuropsychological tests that have been used to date, a review of patients' records in an especially careful manner to control for such things as severity, institutionalization, drugs, etc. is now being undertaken. The test material is being coded and punched. A code has been developed for recording demographic, diagnostic, pharmacological and mental status variables.

Honors: None

Publications:

1. Mignone, R.J., Donnelly, E.F. and Sadowsky, D., Psychological and neurological comparisons of psychomotor and non-psychomotor epileptic patients. Epilepsia, 11:345-359, 1970.

2. Donnelly, E.F., Mignone, R.J., Dent, J.K. and Murphy, D.L., Comparison of Temporal Lobe Epileptics and Affective Disorders on the Halstead-Reitan Test Battery. J. Clin. Psychology, 1971, in press.

Serial No. M-AP(C)-21-2
1. Adult Psychiatry Branch
2. Section on Perceptual and Cognitive Studies.
3. Bethesda, Maryland

PHS-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Studies of Perceptual and Cognitive "Styles" in Psychiatric and Non-psychiatric Subjects.

Principal Investigators: Adolf Pfefferbaum, M.D.

Other Investigators: Monte Buchsbaum, M.D., Richard Stillman, M.D. and Lyman C. Wynne, M.D., Ph.D.

Cooperating Units: Laboratory of Psychology, NIMH

Man Years:

Total:	2.0
Professional:	1.0
Other:	1.0

Project Description:

Objectives:

1) To conduct studies in the field of sensory, perceptual and cognitive functioning in normal and pathological persons and relate sensory and perceptual behavior patterns to their psychophysiologic substrates.

2) To develop and implement computerized measures of perceptual and cognitive functions.

Methods:

A major emphasis is being placed on the use of a biomedical process control computer (LINC). This instrument can be used as both a stimulus producer and a data collector and is, therefore, ideally suited for studies of perception.

Effort has been concentrated in three major areas:

1) The development of average cortical evoked resonse (AER) techniques

2) The development of soft-ware for measuring eye movements on line from a television monitor

3) The development of subject-computer interactive perceptual performance tasks--a series of visual illusion tests.

Major Findings:

1) AER: A sophisticated remotely run computer monitor (CERES) for doing cortical evoked responses has been developed and is being used daily. Utilizing this system, studies have been carried out on the effects of pulse shaping on rapidly stimulated (10 Hz) visual AERs. These results indicate that there is probably both a driving and an on-off stimulus edge component of the AER to these kind of stimuli.

2) A monitor similar to CERES has been developed for a television-based apparatus for monitoring eye movements. In addition the soft ware necessary for dealing with optical abberation and saccadic recognition has been developed.

3) A series of illusions (Muller-Lyer, Ponzo, and Pogendorf) were presented to the subjects first with and then without the illusion producing components by the computer. The subject's responses to the illusion tasks were recorded and analyzed. The susceptibility to the illusion was a stable characteristic with high test-retest reliability. Susceptibility to the illusions correlated significantly with the rod-and-frame measure of field-independence. Field-dependent persons were susceptible to the illusion and field-independent persons were not.

Significance to Biomedical Research and the Programs of the Institute:

The AER technique may be utilized to study individual differences in perceptual responses with the primary advantage of requiring very little subject cooperation and no volitional verbal or motor response is necessary. The subject's task is only to "perceive" the stimuli. It is hoped that this will prove valuable in understanding some of the basic aspects of perception by elimination of the need for frequently confusing verbal reports.

Evaluation of eye movement strategy in visual information input may provide some answers regarding visual perception. This may also lead to better understanding of information processing in general.

Proposed Course of Project:

Several AER projects are in progress including studies of stimulus intensity--AER amplitude relationship to visual field stimulation and site of recording. Another study involves the investigation of AER stability and its relation to perceptual style. A model for dealing with theoretical causes of unstable neurophysiologic responses is being developed.

Publications:

1. Buchsbaum, M., Silverman, J., Henkin, R.I. and Pfefferbaum, D. Contrast Effects on the Auditory Evoked Response and its Relation to Psychophysical judgments. Perception and Psychophysics, in press.

2. Buchsbaum, M.D. and Pfefferbaum, A. Individual Differences in Stimulus Intensity Response. Psychophysiology, in press.

3. Gips, J., Pfefferbaum, A. and Buchsbaum, M. Use of a Small Process Control Computer in a Psychophysiological Laboratory. Psychophysiology, in press.

4. Gips, J., Pfefferbaum, A. and Buchsbaum, M. ERL - A Language for Implementing Evoked Response and Psychophysiological Experiments. Behavioral Research Methods and Instrumentation, in press.

5. Pfefferbaum, A., Buchsbaum, M. and Gips, J. Enhancement of the Average Evoked Response to Tone Onset and Cessation. Psychophysiology, in press.

6. Pfefferbaum, A., and Buchsbaum, M. Handedness and Cortical Hemisphere Effects in Sine Wave Stimulated Evoked Responses. Neuropsychologia, in press.

Serial No. M-AP(C)-21-4
1. Adult Psychiatry Branch
2. Section on Perceptual and Cognitive Studies.
3. Bethesda, Maryland

PHS-NIMH
Individual Project Report
July 1, 1970 - June 30, 1971

Project Title: Perceptual and cognitive style in normal twins.

Principal Investigator: Monte Buchsbaum, M.D.
Adolf Pfefferbaum, M.D.

Other Investigators: Lyman Wynne, M.D., Ph.D.
Winfield Scott, Ph.D.
William Pollin, M.D.

Man Years:

Total:	3.0
Professional:	1.5
Other:	1.5

Project Description:

Objectives:

Evaluation of the heritability and interaction of several sensory, perceptual and cognitive functions in normal volunteer twins.

Methods Employed:

1) Rod and frame measure of field dependence-independence
2) Measure of scanning: direct monitoring of eye movements during a size estimation task
3) Auditory and visual cortical evoked response measures designed to evaluate the effect of stimulus intensity, stimulus constrast, evoked response stability and cortical response symmetry
4) Rorschach inkblot test
5) Psychiatric background interview
6) Clinical rating scales (M-AP(C)-14-1)
7) Blood typing for zygosity (M-AP(C)-16-1).

Major Findings:

Twenty twin pairs have been tested to date. This is too small a sample to draw many conclusions. Preliminary data analysis, however, has revealed some predicted similarities in the monozygotic twins which are not found in the dizygotic pairs. This is particularly apparent for the cortical evoked response wave forms and the stimulus intensity response amplitude functions (augmenting-reducing concept).

Significance to Biomedical Research and the Programs of the Institute:

The concepts of field dependence-independence and stimulus intensity control have been relevant in predicting and explaining individual differences in pain tolerance, sensory isolation, tolerance and response to stimulus overload. Preliminary studies here at NIMH have revealed that there are familial tendencies in perceptual styles as measured by standard psychophysiologic tasks and cortical evoked responses. One method of further elucidating the heritable nature of perceptual style is to investigate several perceptual functions in groups of monozygotic and dizygotic twins. This will allow us to draw some conclusions as to what aspects of perception are genetically transmitted and which ones are learned or modified by environmental experiences.

Proposed Course of Project:

The current project was designed to run for 3 years. This will result in approximately 100 twin pairs tested at the end of that time. This large number is necessary in order to arrive at meaningful and significant conclusions about the objectives of the study.

Honors: None

Publications: None

Serial No. M-CR-10 (c)
1. Child Research Branch
2. Child Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Relations of Preschool Behavior to Earlier Parent and Child Characteristics

Previous Serial Number: SAME

Principal Investigator: Charles F. Halverson, Jr.

Other Investigators: Mary F. Waldrop

Cooperating Units: None

Man Years:

Total: 7.6
Professional: 1.2
Other: 6.4

Project Description:

Objectives:

Our goals are to establish reliable and stable measures of both child and parental behavior, during the early preschool period, to serve as criterion data for the overall branch longitudinal research program, including the periods of early marriage, newborn, and the first year of life. Specifically, the object is to measure personality characteristics, play, social development, assertiveness, cognition, and attentional processes in children two and a half to three years of age, as well as to measure parental variables which affect and may be affected by these child characteristics.

Methods Employed:

The general methodology and procedures of the research nursery school have been described in detail in earlier annual reports. Children in groups of five attend nursery school for four weeks where behavior measures based on direct observations are obtained, in addition to ratings of free and semi-structured play. Our interest is focussed on attentional deployment in two different settings of free play, social behavior towards peers and caretakers, and the nature of assertive behavior elicited by several experimental barrier situations. Intellectual performance is being assessed from several standardized tests and spontaneous speech. The analysis is directed toward the stability

of play and social behavior during the four-week period as well as toward cross-setting generality of the various dimensions. Relations between the various kinds of measures in different settings will provide composite variables which describe general dispositions of the child in the nursery school.

We also collect behavioral data on the parents in a controlled interaction situation. Additional parent data is obtained from interviews and contacts with the mother. These data will be used to check for relations between current parental behavior and the child's functioning in nursery school, as well as to provide criterion data for material gathered on the parents and the marriage at earlier points in time.

Data collection on the main cohort of preschool children from our longitudinal sample has been underway for the last year and will continue into 1973 in order to reach a sample of approximately 65 males and 65 females. This sample is extremely valuable since, for most cases, newlywed data have been acquired on the parents, and the infant and mother-infant pairs have been studied in the first year of life. At the current time, we have seen 45 of the core longitudinal sample. This appears to be about one third of the core sample that we anticipate can be seen. Case loss in the first year (moving out of the area, unable to contact, illness, etc.) has been running at about 25 percent.

By the use of several computer programs, we are able to monitor continuously the cumulative reliability and stability of both our observational procedures and the teacher rating material. In addition, these programs provide for accurate storage and retrieval of nearly all the preschool data in the longitudinal study.

Major Findings:

During the past year, we have devoted some time to the analysis of results from a longitudinal sample which was studied preparatory to the main cohort. In this study children who had been seen previously as newborns and in the research nursery school at two and a half were followed up at age seven and a half with a battery of cognitive tests and an assessment of play behavior.

This year, at a symposium of the Society for Research in Child Development, we communicated the relations between active, assertive attack on experimental barriers in the preschool period and three domains of functioning at age seven and a half (cognitive, social, and play). It was found that children who were effective and assertive in barrier situations later, at seven and a half, were the ones who (a) had higher verbal intelligence and showed more imagination in play (cognitive domain), (b) were more dominant in initiating peer contacts and were more at ease with peers (social domain), and (c) were more vigorous, less fearful and coped with new situations (play domain). Also there were longitudinal stabilities of vigor and lack of fear as well as continuities in peer behavior between the two periods. Through an analysis of the longitudinal data for barrier behavior, we have arrived at a

better understanding of some of the cognitive and personality-social behaviors relevant to coping with barrier situations in the early preschool period.

In the additional papers to be presented this fall at a symposium of the American Psychological Association, we will report the finding that three measures of free play, in addition to WISC verbal intelligence and social maturity, were related to verbal communication at two and a half. The first measure, Exploring, consisted of the percentage of time spent shifting between play settings. The other two free-play measures describe the pace of the shifting, one consisting of the mean length of each shift bout and the other the mean rate of shift bouts in feet traversed per second. These latter two variables were negatively related and can be considered as describing a dimension with fast, deliberate shifts at one end and slower, more indirect shifts of activity at the other.

For both sexes, preschool verbal communication was positively related to verbal IQ, social maturity, and the measure of free play exploration at seven and a half, with high verbal males and females being higher in verbal IQ, social maturity, and in amount of time exploring the free play environment.

Longitudinal sex differences were obtained for the pace measures: verbal communication at two and a half was positively related to slower-paced, deliberate shifting in males, but negatively related for females. High verbal males showed slower, more indirect shifts, while high verbal females shifted quickly and directly between play settings. Analyses of other segments of this preparatory study are still underway and reports will be prepared on other aspects of the data as the analyses are finished.

Significance to Bio-Medical Research and the Program of the Institute:

The identification of stable patterns of preschool behavior in the areas of assertiveness, response to caretakers, interaction with peers, and cognitive performance is important for the description of normal development of children. The present cohort will provide valuable ways of documenting varities of preschool behavior, as well as clues to the origins of these behaviors in the data collected earlier on these same children and their parents. The planning of mental health programs, both diagnostic and remedial, will depend on such reliable information about development.

Proposed Course of the Project:

Data collection has been underway for one year, and will continue for two more years. An additional year or two will be necessary for the reduction and analysis of the vast amount of data obtained. Analyses of the preparatory study will continue and further reports will be prepared.

Honors and Awards: None

Publications: None

Serial No. M-CR-11 (c)
1. Child Research Branch
2. Infant Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Relations between Human Neonatal Behavior and Later Development

Previous Serial Number: Same

Principal Investigator: Raymond K. Yang

Other Investigators: Richard Q. Bell

Cooperating Units: None

Man Years:

Total: 4.75
Professional: .75
Other: 4.00

Project Description:

Objectives:

This is a psychophysiological and behavioral study of human neonates, designed to provide measures of stable individual differences reflecting congential characteristics of infants born to families in the branch longitudinal study. The data are to be used to identify congenital contributors to later development as well as the manner in which congenital factors interact with parental characteristics in producing later outcomes.

Methods Employed:

This section is currently analyzing data collected during the last three fiscal years. Approximately 140 newborn infants were studied. Each infant was observed in a hospital nursery and continuous recordings of selected psychophysiological and behavioral functions were obtained during two consecutive interfeeding periods between 50 and 72 hours of age. The functions and responses recorded were: the electrocardiogram; respiratory waveform; galvanic skin potential; electro-oculogram; skin temperature; body motility; tactile threshold; a righting reflex (the prone head response); characteristics of non-nutritive sucking; the reaction to interruption of sucking; and physiological and behavioral changes due to swaddling.

The section has also completed a monograph on a previous study of 75 newborns, 55 of whom were followed up to age 2-1/2 years in order to test procedures and obtain some indication of whether congenital factors measured in the newborn period would be related to later characteristics, when the main longitudinal study was carried out. The behavior measures found to be predictive in this preparatory study were incorporated in the main longitudinal series started in 1967 and, on the basis of the predictive value of the single physiological measure (respiration rate), other physiological measures were included, as described above.

Major Findings:

In brief the monograph reports that rapidly breathing, highly sensitive, and responsive newborns were later found to be lethargic preschoolers who watched others rather than participate in the free play and games. These preschoolers were less vigorous in coping with barriers to their ongoing activity, and were less verbally communicative than their counterparts who were not as sensitive and responsive as newborns. The general trend of the findings was that there was an inversion of intensity between periods, early high rate, speed or magnitude of response being associated later with low intensity of behavior. Of the two follow-up studies from the newborn period other than our own to produce defensible evidence of prediction from the newborn period (five reported negative or inconclusive results) one reported a finding that paralleled ours, the other reported a relation involving continuity rather than inversion of intensity between periods. However, the latter findings applied to only a limited range of behavior on one sub-sample.

Since the completion of data collection on the main longitudinal series in May of 1970, it has been possible to conduct preliminary analyses of inter-rater reliability and test-retest stability. These analyses, conducted by hand on small (n = 10 to 20) randomly selected samples indicated that: 1) Inter-rater reliabilities for the prone head response and sucking behaviors were acceptable (range of product-moment correlations $\bar{r}$ = .77 to .97); 2) Percentage of agreement between raters for the major physiological measures (heart rate and respiration rate) was 100 percent; 3) Percentage of agreement for four state ratings ranged between 69 and 97 percent; 4) Percentage of agreement between raters for the major behavioral measures ranged from 32 to 80 percent. (The percentages for physiological and behavioral measures were based on the number of agreements regarding the presence of the measure during consecutive one-minute intervals; they are conservative estimates of actual agreement).

Stability of individual differences between two feeding periods was the next concern. The effects of swaddling on the infant, measured as the extent of quieting, was found to lack test-retest reliability between two adjacent swaddlings (approximately 4 minutes apart) and two test periods (approximately 8 hours apart). Crying in response to a painful stimulus was fairly stable between two test periods approximately 8 hours apart

(product-moment r = .71). Behavioral responses to the air-jet tactile aesthesiometer were of insufficient test-retest stability for use as a stable measure of newborn functioning. Current analyses are being conducted to evaluate the stability of autonomic responses to the aesthesiometer. Analysis of other measures is proceeding.

Significance to Biomedical Research and the Program of the Institute:

The results to date indicate that there are some clues to later development that can be seen in the repertoire of the newborn. This answers a very basic theoretical question. The nature of the clues uncovered from the newborn period, if corroborated in our further studies, will require a basic change in thinking about what is prognostically "healthy" behavior in newborns. Signs of viability in the first few minutes of life (vigorous respiration, reflex responsiveness) may not be a basis for extrapolation as to what is optimal behavior in the remainder of the newborn period.

Proposed Course of the Project:

During the next year we should complete the analysis of the most important behavioral data, and in the next two years, the physiological data. At that time it should be possible to analyze and report on relations between these newborn measures and later behavior at three and eleven months postpartum, the latter recorded by one other team in the longitudinal study. Relations between newborn and preschool characteristics cannot be determined until 1975, since data gathering at this later phase will not be completed until 1973, and reduction of the data will not be completed until two years later.

Honors and Awards: None

Publications:

Bell, R.Q., Weller, G.M., & Waldrop, M.F. Newborn and preschooler: organization of behavior and relations between periods. Monogr. of the Soc. for Res. in Child Develpm., 1971, in press.

Serial No. M-CR-12 (c)
1. Child Research Branch
2. Section on Family Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Developmental Patterns in the Young Family

Previous Serial Number: SAME

Principal Investigator: Robert G. Ryder

Other Investigators: David H. Olson, John S. Kafka, and Walter Sceery

Man Years

Total:	6.0
Professional:	3.4
Other:	2.6

Project Description:

Objectives:

To describe and formulate the topography of variation among young married couples; to describe and explicate the developmental history of differing patterns of relationships; to integrate sub-cultural, social, psychological and personality phenomena into a comprehensive view of intimate human relationships; to investigate correspondence among marriage patterns, attributes of offspring and patterns of parent-child interaction.

Methods Employed:

Data presently being studied was previously collected from a sample of 2,162 young married couples from the Washington, D.C. metropolitan area. Efforts are presently underway to reduce data, to set up a computer data retrieval system, and to otherwise generate data files maximally suitable for further analyses. Statistical and other numerical procedures are also being used to perform substantive analyses upon portions of the available data including interaction procedures, self-descriptive adjectives provided by subjects, narrative self-reports, and questionnaires.

Present data collection is limited to marriage follow-up studies of couples whose children have reached the preschool phase of the Branch longitudinal study, a group of about 40

couples so far. Data collection includes interaction procedures, questionnaires and an interview.

Major Findings:

In questionnaire data, the main completed analysis is of the self-report Spouse Adjective Test (SPAT), for which a statistically stable dimensional structure has been established. Dimensions seem to include such attributes as reported irritability, romantic feeling, social extraversion, and content related to cognitive control.

Another analysis of questionnaire data, presently underway, concerns the effects on self-reported marriage satisfaction of having a child. Results so far suggest that findings previously reported in the literature may exaggerate the extent to which having a child is related to lowered marriage satisfaction. It presently appears that the effect may be modest or even not significant, or may be restricted to variables relating to the amount of attention paid by one spouse to the other.

Couples' autobiographical narrative sketches ("marriage histories") have been coded for about half of all cases. A procedure for organizing this data has been devised, and may have fairly general applicability in situations where unstructured or narrative material is collected and subjected to an extensive coding system. The procedure is called the Qualitative Unusual Event Sorting Technique (QUEST), and is designed for situations in which codes or attributes may include either (a) many codes each of which is used only infrequently, or (b) codes which are similar in some way but which may never occur together, e.g., "laughs" and "chuckles." QUEST clusters a pair of attributes on the basis of their occurrence in similar contexts, rather than on the basis of their occurrence together. Preliminary analyses are presently complete using QUEST with strings of terms provided by spouses for describing their marriages, and suggest such variables as marriage success by working to overcome problems, marriage success by experiencing intense or romantic feelings, and marrriage success by mutual sharing and companionship.

Analysis of the Color Matching Test interaction procedure is now close to completion. Adequate inter-rater reliability and adequate intra-test reliability have been established. A dimensional analysis based on 430 couples suggests further refinements of dimensions previously reported. Present dimensions include one of rationality in style of discussion, one of affect expression, one of questioning the presented test structure, and two dimensions related to who "wins" in the discussions which occur during this procedure. Adequate inter-rater and intra-test reliability have also been established for

the more recently devised interaction procedure called the Inventory of Marital Conflicts.

Several integrative and conceptual efforts relating to general concerns of this project and to previously described work have reached the publication stage. David Olson has completed a comprehensive review of marital and family therapy. John Kafka has completed a radical reformulation of double bind theory which, to paraphrase one discussant, stands the original theory on its head. A conceptual framework for describing married couples, based now on interview reports from 300 couples, has also been published, as has a theoretical formulation of the interpersonal dynamics of courtship and the marriage transitional process.

Significance to Bio-Medical Research and the Program of the Institute:

From the growing interest in this project displayed by those in the marriage and family field, it is clear that both the substantive findings and the methodological innovations developed here will be generally utilized. For example, if only a minimal effect on marriage satisfaction is found due to having a child, conclusions based on several earlier studies will have to be modified. The new self-report adjective measure in couples' own terminology (SPAT) is an innovation which might be of use elsewhere. The Inventory of Marital Conflicts is an easily utilized procedure which is already in high demand in this country and abroad. The several recent conceptual papers have drawn reactions suggesting that they are thought to be of importance by other groups. The double bind reformulation in particular may represent a theoretical breakthrough in conceptualizing intimate relationships.

The overall significance of the project continues to be in the development of a differentiated view of intimate relationships which might be useful to those dealing clinically or by way of research with married couples, and in cooperating with other projects in the Branch in attempting to demonstrate predictive relationships between young married couples and their subsequent offspring.

Proposed Course of Project:

Activities for the coming fiscal year will continue to consist primarily of working with the data in hand. Quantitative and quasi-clinical studies, studies of particular relationship patterns, and comprehensive studies of dimensionality are to be carried forward with a view to eventual integration.

Honors and Awards: NONE

Publications:

Olson, D. H.: Marital and family therapy: Integrative review and critique. J. Marr. and the Fam. 32: 501-538, 1970.

Olson, D. H. and Ryder, R. G.: Inventory of marital conflicts: An experimental family interaction technique. J. Marr. and the Fam. 32: 443-448, 1970.

Olson, D. H.: The family professional: The past, present, and future. Fam. Coordinator (in press).

Kafka, J. S.: Ambiguity for individuation: A critique and reformulation of double bind theory. Arch. Gen. Psychiat. (in press).

Ryder, R. G.: A topography of early marriage. Fam. Process, 9: 385-402, 1970.

Ryder, R. G., Kafka, J. S., and Olson, D. H.: Separating and joining influences in courtship and early marriage. Am. J.Orthopsychiat. (in press).

Serial No. M-CR-22(c)
1. Child Research Branch
2. Infant Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Offspring Effects on Parents

Previous Serial Number: Same

Principal Investigator: Richard Q. Bell

Other Investigators: Lawrence V. Harper, University of California at Davis

Cooperating Units: DCRT, Computation and Data Processing Branch

Man Years:

Total:	1.0
Professional:	.5
Other:	.5

Project Description:

Objectives:

To review the literature for evidence of offspring effects on parents; to provide a conceptual scheme to organize findings; to initiate studies in areas crucial to theories of early development.

Methods Employed:

Literature search, concept development, and development of research methods relevant to offspring effects on parents.

Major Findings:

Current work represents a continuation of efforts to develop parallel reports on findings from human and infra-human species clarifying the effects of offspring on parents. The principal investigator has published previous reports on (1) a revision of theories of socialization within the human family, and (2) a collation of data from several studies indicating the extent to which stimuli from infants and children control parent behavior. Lawrence Harper has published papers showing that (1) there is evidence requiring a revision of the notion of uni-directional effects from parents to mammalian young, and (2) that there is an abundance of data showing mammalian offspring provide exogenous stimuli facilitating or inhibiting parent behavior in all the major classifications under which we expect stimuli to be effective.

In the theoretical paper listed below, published this year, Harper was not only able to show that the effects of parents on offspring had been overestimated in studies of many animal species, but that the young may have had a role in mammalian evolution that seems to have been largely overlooked up until the present. Harper developed evidence that the innovative activity of the young affects the adaptive radiation of species into new environments. The exciting implications of this paper, and the response by experts in the field of animal behavior, has led Harper to undertake a new work this year exploring a similar theme at the human level.

The principal investigator has prepared a paper for a World Health Organization conference on adaptation and stress, developing the theme that the contrast between the apparent helplessness and dependency of the young, on the one hand, and their impelling and controlling effect on parents, on the other hand, operate to produce a special kind of stress. For those who might otherwise underestimate the magnitude of this stress, the paper cites research showing that the stimulus characteristics of the child have played a surprisingly important role in the "battered child" syndrome, cases of serious physical injury inflicted on children by parents. The paper advocates an interactional view of child rearing, from which parents would expect to be modified themselves, and sometimes stressed, by the variable, energetic, and novel behavior of the young. This interactional view is needed to counteract major thought movements that have unwittingly aggravated rather than ameliorated stress on parents, movements such as education philosophy, behaviorism, and psychoanalysis.

In a previous paper, the principal investigator briefly described new research approaches that could be used to isolate effects of parents and children on each other. Several dissertations have since been carried out at other institutions following these suggestions. Accordingly, it appears that a more complete review of available research approaches could serve a valuable stimulating and guiding function. A paper is now being prepared that lists several research approaches, each having a different pattern of advantages and disadvantages relative to (1) ability to isolate effects of participants in the system and (2) limits on generalization that result from procedures or samples required by the approach. A very simple but valuable insight gained from reactions to a first draft of this paper at a recent colloquium was that a modification of existing experimental procedures would provide a research approach with a unique pattern of advantages. By instructing parents to carry out certain experimental procedures with their own children in a controlled laboratory setting (procedures that have been customarily carried out by experimenters with children) one would be able to preserve experimental control over the independent variable of parent behavior, while still being able to generalize to natural parent-child pairs. The paper also reviews approaches to manipulating child behavior as an independent variable. In order to produce effects on the behavior of adults, one of these approaches utilizes children trained in role-playing. In one other approach, the experimenter simulates a series of child responses to an adult, in a situation in which a child's presence provides elements of "naturalness", but the child is not actually the source of stimuli to which the adult reacts.

Returning to empirical work in our own laboratory, efforts to locate hierarchies of sequentially ordered infant and maternal behaviors from home observation data between the first and ninth week of life have reached a final stage this year. Mr. Ray Danner of DCRT completed a computer program for analyzing sequential, temporal contingencies in mother-infant interactions. This program supplied us with frequency distributions for all events following a reference infant or maternal behavior at various intervals. We are now sifting through these data, and the first impression is that we should be able to locate two or more sequentially ordered sets of infant responses even at this early age. If this proves to be the case, as our analyses proceed further, it will be possible to provide further empirical support for a theory advanced in a previous paper (Stimulus Control of Parent or Caretaker Behavior by Offspring) that infants and parents respond to each other not only in terms of single events but also in terms of each other's repertoires. Identification of early repertoires may also make it possible to trace the process by which hierarchies of parent and infant behaviors develop in the first few weeks of life.

Significance to Biomedical Research and the Program of the Institute:

This series of conceptual, methodological and empirical contributions is intended to bring about a revision of socialization theory and research methods that have, in the main, proved relatively unproductive in recent years. The revised approach may make it possible to launch socialization research on a course that corresponds better to the realities of parent-child interaction, and thus has more likelihood of generating consistent results than has past efforts. Socialization research is, in turn, the basis for advice to parents as well as many social and family oriented action programs.

Proposed Course of the Project:

After the completion of Lawrence Harper's paper on the impact of the young in human society, and the paper on research approaches for isolating parent and child effects, all papers from the project will be drawn together, along with contributions from other authors, in a volume of readings on the effects of the young on their parents.

Honors and Awards: None

Publications:

Harper, L. V. Role of contact and sound in eliciting filial responses and development of social attachments in domestic guinea pigs. J. Comp. Physiol. Psychol., 73: 427-435, 1970.

Harper, L. V. Ontogenetic and phylogenetic functions of the parent-offspring relationship in mammals. In Lehrman, D. S., Hinde, R. A., and Shaw, E. (Eds.), Advances in the Study of Behavior, New York: Academic Press, 1970.

Serial No. M-CR-23 (c)

1. Child Research Branch
2. Section on Parent-Child Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Determinants and Dimensions of Mother-Infant Interaction

Previous Serial Number: Same

Principal Investigator: Howard A. Moss

Other Investigators: Sandra J. Jones

Cooperating Units: None

Man Years:

Total:	5.00
Professional:	2.00
Other:	3.00

Project Description:

Objectives:

The major objectives of this research are to identify primary dimensions of mother-infant interaction, to illuminate the determinants of these interaction patterns, and to relate these findings to data provided by other components of the Branch longitudinal program, including the early behavioral makeup of the infant, the preparental relationship of the mother and father, and the mother's early experience with her own family. In addition, the data obtained from the mother-infant study will be used to predict nursery school behavior when the children are studied at 2½ years of age.

Methods Employed:

The data collection for this project on mother-infant behavior was initiated in September, 1967 and completed by October, 1970. Although most of the reliability data was collected throughout the course of the study, there were some cases studied through January, 1971, for the purpose of obtaining additional reliability information on some of the procedures. The sample consists of about 120 mother-infant pairs from the second cohort of the Branch's longitudinal program.

All the procedures administered in the main longitudinal study of mother-infant interaction have been described in detail in previous annual reports.

Therefore this annual report will only provide a summary.

(1) Interviews and questionnaires were administered to the expectant mother during the last trimester of pregnancy.

(2) Two six-hour home observations were made of mother-infant interaction at three months of age.

(3) Postpartum interviews and questionnaires were administered to the mother when the infant was about 3½ months of age. While these procedures were administered to the mother, the infant was studied in a laboratory situation using procedures that involved vocal conditioning, visual attention, resistance to cuddling, and muscle tonus.

(4) When the child was eleven months of age, observations in the home dealt with reaction to strangers, separation from the mother, imitation, socialization, exploratory behavior, etc.

In addition, we are conducting two six-hour home observations of mother-infant interaction at three months of age for a subsample of approximately 40 second-born infants for whom we already have such data on the first-born. This study will permit us to assess differences in maternal behavior toward first- and second-born children, using the mother as her own control. The data have been collected on 24 of these second-born cases.

The majority of the staff effort for the past 6 months has been devoted to coding, processing, and carrying out preliminary analyses of data. A contract was arranged with Dr. Elizabeth Hillenbrand to make ratings from tape recordings of interviews. The principal investigator conducted both the pregnancy and postpartum interviews, but only made ratings of the pregnancy material. Dr. Hillenbrand is rating the postpartum interviews. This arrangement allows us to maintain independence of rating between these two sets of data. Dr. Hillenbrand rated 20 of the pregnancy interview tapes for the purpose of establishing the reliabilities of the ratings. The principal investigator, in turn, is making reliability ratings on a number of the postpartum interview tapes. The inter-rater reliability coefficients for the pregnancy interview variables ranged from .64 to .98, with a mean reliability of .82.

The codes obtained from the two six-hour home observations for the 120 cases have been put on IBM cards and from these cards we have derived the scores for each case for the 46 home observation variables which were studied. Reliability coefficients, obtained by correlating the scores from the first home visit with scores from the second home visit, ranged from .03 to .93 with a median correlation of .82. The scores on the 46 variables were, in turn, combined for the two home visits. Inter-rater reliabilities were obtained by having the observers working in pairs and coding the home observation variables on a separate sample of cases interspersed among the regular observations. Every reliability case was seen by each possible combination of pairs of the three observers. These reliabilities ranged from .00 to 1.00 with a

median correlation of over .95. On the basis of the test-retest and inter-rater reliability data, 5 of the 46 home observation variables will be omitted from further analyses.

A principal components factor analysis was conducted on the home observation scores in order to obtain a reduced and more robust set of measures. This analysis resulted in five rotated factors, accounting for a major amount of the variance for both male and female subsamples. A future step will be to derive factor scores for each of these factors for our sample of subjects. These scores will provide basic data which can be related to other measures in both our cross-sectional and longitudinal analyses. Our home observation data also will be used to derive conceptually meaningful combination and contextual scores. This will involve special computer programming aimed at deriving scores for these conceptually developed variables.

In addition, data preparation has proceeded for the pregnancy and post-partum questionnaires, the traditional family values questionnaire, the interviews, and laboratory studies on vocal conditioning, muscle tonus, and visual attention. The vocal conditioning data have been partially analyzed. These data were collected in order to determine whether individual differences in the rate of conditioning to "social" stimuli are related to antecedent data collected in earlier phases of the study on mother-infant interaction. Illustrations of the first findings to appear from the within-stage analyses of these data are: males exhibited a higher rate of responding on measures of vocalizations, smiles, and eye contact with the experimenter than did the females; females proved to be more responsive than males to contingent social reinforcement. In addition, it was found that infants' smiles occurred more frequently during eye contact with the experimenter than did vocalizations.

Significance to Bio-Medical Research and the Program of the Institute:

The data collected from this project should provide basic information concerning the extent to which initial response tendencies in infants and various parental characteristics conjointly contribute to early mother-infant interaction patterns. From these data we can begin to determine the variance in the mother-infant interaction that is attributable to infant characteristics, as well as the variance associated with particular maternal predispositions. The results of these studies should also help us understand the development of the mother's and infant's attachment toward one another; the emergence of social behavior and responsiveness in the young child; some of the developmental antecedents of cognitive functioning, and generally should provide information concerning the basic dynamics of early personality functioning.

Proposed Course of Project:

Data processing will continue for this coming year. This will include rating, coding, and key punching of all material and the construction of the final set of variables to be used in the cross-sectional and longitudinal analyses. We also expect to complete all within-stage analyses of the mother-infant material. We are continuing with our data collection on the second-born sample and expect to have this study completed within the coming year.

Honors and Awards:

None.

Publications:

Moss, H. A. & Robson, K. S. The relation between the amount of time infants spend at various states and the development of visual behavior. Child Development, 41: 509-517, 1970.

Jones, S. J. Children's two-choice learning of predominantly alternating and repeating sequences. Journal of Experimental Child Psychology, 10: 344-362, 1970.

Jones, S. J. & Moss, H. A. Age, state, and maternal behavior associated with infant vocalizations. Child Development, In Press.

Serial No. M-CR-24 (c)
1. Child Research Branch
2. Child Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Structure and Correlates of Preschool and Child Behavior

Previous Serial Number: SAME

Principal Investigator: Charles F. Halverson, Jr.

Other Investigators: Mary F. Waldrop

Cooperating Units: Section on Twin and Sibling Studies, Adult Psychiatry Branch, NIMH [M-AP-(C)-19-6]

Man Years:

Total: 1.2
Professional: .8
Other: .4

Project Description:

Objectives:

To organize and describe patterns of behavior and individual differences in young children through experimental and naturalistic studies at various age periods in the preschool and early school years. These studies expand and explore in detail certain hypotheses derived from the main longitudinal study of behavioral development.

Methods Employed:

Various samples of preschool and early school-age children are intensively studied in free play, and in special experimental situations. For example, extensive samples of free play are taken to describe behavioral tempo and impulse control. Experimental parent-child interactions are observed to aid in delineating patterns of maternal-child behaviors associated with these variables. Depending on the hypotheses to be explored, children are given standardized developmental tests of behavioral and cognitive performance and parents are interviewed about salient concepts.

Major Findings:

Activity on this project has been curtailed this year because our staff

has been heavily involved in the intensive data collection phase of the nursery school segment of the on-going longitudinal study. Both staff and facilities have been largely unavailable for intensive study of separate samples.

Previous reports have described studies relating the cumulative incidence of minor physical anomalies to hyperactive, fast-moving behavior in selected samples of young children. Data collection and analyses are now underway on the developmental course of the anomalies from birth to two and a half years of age, as well as the relations to various patterns of play and social behavior at the latest of these ages. A study reporting replications of the anomaly-hyperactive findings on three different samples of children has been accepted for inclusion in a book of readings about development. Planning is now underway to check further, on other samples, the extent and significance of the relations between anomalies, hyperactive behavior, and other variables of cognitive and social behavior.

A paper has been prepared for publication describing the varieties of preschool play behavior related to mechanically recorded bodily activity. The activity was recorded by a simple device consisting of a packet of three modified small wristwatches worn on the children's backs during outdoor free play. The bodily movement recorded by these devices was found to be quite highly related to active, vigorous play for both boys and girls in an outdoor setting, indicating that the recorder was validly measuring a vigorous active type of play. The recorder data were related to play activity in an indoor setting and it was found that boys who tended to be motorically active outdoors tended to be the same in indoor play. The outdoor recorder data were significantly related to 9 of 14 objective measures of gross activity indoors. For females, little generality across situations was found: only 3 of the 14 relations were significant. Males, in addition to being significantly more active in their play, tended also to be consistent across outdoor and indoor play, whereas for females, play activity outdoors was relatively independent of indoor play. The vigorous play of girls tended to be setting-specific while for males this vigorous activity showed more generality.

An analysis of teacher ratings showed that gross motor activity for both boys and girls was highly related to nearly all the ratings teachers made of behavior, 21 of 27 ratings being significantly correlated to the activity recorder data. Apparently, components of play measured by the activity recorder are of major importance for teacher's conception of young children. These data are in line with our earlier studies indicating that one of the most important areas that can be studied in two-and-a-half-year-old children is vigor and intensity of play. These data also provide, on one hand, a valuable validity check for ratings concerned with vigorous, active play and, on the other, the caution that if we had used teacher's ratings alone, no distinctions would have been found between the sexes in the situational variability of play activity.

We are also continuing a collaboration begun in the last year with the Section on Twin and Sibling Studies of the Adult Psychiatry Branch, NIMH [M-AP-(C)-19-6]. We study sets of twins that are part of a study of the early

congenital and experiential contributors to development. To date we have assessed five pairs of twins in a cohort of ten pairs intensively studied from birth to ages three and a half to four years. The plan is to relate nursery school behavior to data collected by that section on genetic, physiological and behavior variables during the early years.

Significance to Bio-Medical Research and the Program of the Institute:

The several different developmental patterns associated with hyperactive, impulsive behavior and minor physical anomalies may provide some evidence about the early or congenital contributors to impulse-control problems and significantly aid in their early diagnosis, treatment, and management. The understanding of early developmental processes can lead to appropriate early intervention that would be more effective than diagnosis and treatment occurring at a much later point in time. Studies of twins and behavioral activity in the preschool period provide additional evidence of the interface between genetic, physiological, and behavioral dimensions.

Proposed Course of the Project:

Data will continue to be collected on the minor physical anomalies from birth to two and a half. Stability analyses are now underway. Studies of the cohort of twins in our nursery school procedures will also continue during the coming year. Planning for other studies of hyperactivity, motoric activity and behavioral development will be initiated and some pilot work undertaken.

Honors and Awards: None

Publications:

Waldrop, M. F., and Halverson, C. F., Jr.: Minor physical anomalies: their incidence and relation to behavior in a normal and a deviant sample. In Smart, R. C., and Smart, M. S. (Eds.): Readings in Development and Relationships. New York, MacMillan, 1971, in press.

Waldrop, M. F., and Goering, J. D.: Hyperactivity and minor physical anomalies in elementary school children. Amer. J. Orthopsychiat. 41: 1971, in press.

Serial No. M-CP(C)-18-3
1. Laboratory of Clinical Psychobiology
2. Section on Clinical Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biochemical and Pharmacological Studies of Sleep

Previous Serial Number: Same

Principal Investigator: Frederick Snyder, M.D.

Other Investigators: William E. Bunney, M.D., David H. Fram, M.D. J. Christian Gillin, M.D., Frederick K. Goodwin, M.D., Leonard S. Jacobs, M.D., Robert M. Post, M.D., and Richard J. Wyatt, M.D.

Cooperating Units: Laboratory of Clinical Science, CBR
Laboratory of Clinical Psychopharmacology, SMR

Man Years (1970):

Total:	3
Professional:	1 1/2
Other:	1 1/2

Project Description:

Objectives:

Experimental findings over the past several years promise understanding of the basic biochemical processes underlying sleep, and over the same period increasingly clear demonstrations of the severity of sleep disturbances in many psychiatric patients indicate the need for better means of alleviation. These practical and theoretical aspects are closely linked, for if biochemical understanding of sleep could be achieved, rational treatment of its disturbance would surely follow.

The work of Jouvet and others in cats suggests that non-REM sleep is somehow related to serotonin metabolism, while REM sleep has a particular relationship to norepinephrine. Among the evidence for these conclusions is a specific reduction in non-REM sleep after parachlorophenylalanine (PCP) administration, as well as the specific reduction of REM sleep by monoamine oxidase inhibitors (MAOI). Pro-

vocative as these findings are, their human relevance was uncertain so long as comparable studies had not been carried out in man, and this has been the primary aim of our own efforts over the past several years.

Contrary to findings in the cat, we have reported that therapeutic doses of parachlorophenylalanine (PCP), an inhibitor of serotonin synthesis, produces marked suppression of REM sleep without diminution of total sleep, an effect which is reversed by 5-hydroxytryptophan (5-HTP) the serotonin precursor which by-passes the PCP inhibition of serotonin synthesis. On the other hand, we have found that inhibitors of catecholamine synthesis, alpha methyl paratyrosine (AMPT) or alpha methylphenylalanine (AMPHe) have the effect of elevating REM sleep levels without significant change in non-REM sleep. We have found that oral dosages of L-Dopa, presumably elevating central Dopamine concentrations, also diminish REM sleep. Thus, both serotonergic and adrenergic systems would appear to influence the occurrence of REM sleep, but in ways quite opposite to those implied by previous studies in the cat.

While the main implications of these findings are being pursued by Dr. Wyatt at his new sleep laboratory in the Laboratory of Clinical Psychopharmacology, SMR, several related issues have been followed up here during the past year in a number of separate studies.

Patient Material:

20 patients
10 normal controls

Methods and Findings:

A. Effects of Intravenous L-Dopa given During Sleep

Ten depressed patients were given infusions of L-Dopa and a pH matched placebo during REM and non-REM sleep. Patients were monitored for a total of 139 nights with EEG, EMG and EOG, and slept with a forearm intracatheter attached to a 10-ft polyethylene tube that extended outside their room. A dilute heparin saline solution (10 μ/cc) kept the I.V. from clotting. A selective inhibitor of decarboxylase in the periphery, alpha-methyl-DOPA-hydraxine, was started 3 days prior to infusions at doses of 250 mg B.I.D. for the DL-form (MK485) and 50 mg T.I.D. for L-form (MK486) in order to potentiate central and minimize peripheral effects of L-Dopa.

Infusions of L-Dopa (25-50 mg in 20 cc vial given over 2 minute periods) during non-REM sleep significantly increased the REM latency (sleep time before the first REM); 71.4 minutes--Dopa vs 44.3 minutes--placebo ($p < .05$, paired t-test).

Given at the onset of the first rapid eye movement of a REM period, L-Dopa significantly shortened the first REM period; mean REM time 9.3

minutes--Dopa vs 17.7 minutes--placebo ($p < .05$, paired t-test). The pre-REM Dopa infusions did not significantly shorten the length of the first REM period. Five patients who also received infusions at the onset of the second REM period demonstrated a decreased total length of the REM period after L-Dopa; 20.7 minutes--L-Dopa vs 43.3 minutes--placebo (p .05, paired t-test).

While the first REM period was significantly shorter after Dopa administration, there was a trend toward a compensatory rebound during the second REM period when no infusion was given; 30.5 minutes--Dopa vs 23.4 minutes--placebo. There was no overall effect of the brief infusions on either total REM or total non-REM sleep.

Thus, L-Dopa appeared to acutely affect two aspects of the REM mechanism: both delaying the onset of REM sleep and inhibiting the maintenance of the REM episode once it is generated.

B. Effects of Histidine on Sleep

Histamine has been implicated as a possible "waking factor" in a number of studies. To examine such a possibility L-histidine, the amino acid precursor of histamine, was given to three narcoleptic patients in dosages up to 20 grams/day for up to two weeks while serial nightly sleep records and periodic all-day records were obtained and compared with control records obtained before and after. No differences between drug and placebo periods were found for total sleep, amount of nighttime waking, daytime sleep, REM sleep or delta (stages 3 and 4) sleep. It is possible that the hypothesized action of histamine was masked by effects of the histidine itself or those of other metabolites also resulting, but this exploratory study does not encourage the possibility that histamine is particularly implicated in the biochemistry of sleep or waking.

C. Effects of Prednisone on Sleep

Both sleep disturbance with special attrition of REM sleep and elevated adrenal corticoid steroid excretion have been shown to occur under similar circumstances and over similar time courses during periods of particular psychic distress in depressed and schizophrenic patients. For that reason we were prompted to examine whether glucocorticoid steroids themselves might have any effects on the EEG sleep pattern.

Ten healthy, normal volunteers, aged 18-21, were each studied for 10-14 consecutive nights following two nights of adaptation to sleep recording. The subjects received the same number of identical capsules each day six hours before bed time in the following schedule: Baseline period (4-7 nights, placebo), Drug night #1 (prednisone 60 mg, 20 mg, or 5 mg), Intervening night placebo), Drug night #2, Recovery nights (3-4 placebo). Subjects were allowed 8 hours in bed each night. Sleep records were evaluated without knowledge of drug status.

The results strongly suggest that both 50 and 20 mg doses of prednisone significantly reduce total REM sleep ($p < .001$) and increases REM latency ($p < .01$); rebound elevation of REM time occurs for the three day recovery period. While NREM sleep seemed to change inversely with REM sleep, this effect was not statistically significant. There was no significant change in delta sleep, sleep latency, or early morning awakening; on the two drug nights there was a trend towards increased intermittent awakenings, 3.6 min and 8.4 min, respectively, compared to the baseline average of 2.7, but these changes were not significant. Significant effects have not been statistically found thus far after the 5 mg dosage, though a trend in the same direction is apparent. Comparable REM suppressive effects have been demonstrated over four day periods in three depressed patients given prednisone in therapeutic trials, even though there were no apparent behavioral effects.

D. Measurement of Phasic Integrated Potentials (PIP) during Treatment with Parachlorophenylalanine

So-called ponto-geniculo-occipital (PGO) spikes have been of great importance in the feline neurophysiological studies of REM sleep and figure in some recent speculations about the possible involvement of REM sleep in schizophrenic illness. Dement and his coworkers find that when REM sleep is suppressed by parachlorophenylalanine (PCP) the PGO spikes normally confined to REM periods begin to appear throughout sleep and during intervals of waking coinciding with 'hallucinatory-like' behavior. It would be a matter of major importance, therefore to be able to study PGO spikes in humans, and Rechtschaffen at Chicago has recently described a measure, the phasic integrated potential (PIP), which he believes to be a human analogue of the PGO spike obtainable from surface recording around the eyes. In collaboration with Dr. Richard Wyatt, now of the Laboratory of Clinical Psychopharmacology, SMR, and with Dr. David Horwitz of NHI we have set out to determine whether human PIPs increase during non-REM sleep or waking after PCP treatment as PGOs do in cats.

Thus far sleep PIPs have been measured in two patients with severe migraine headaches given PCP as a possible therapy. Prior to PCP administration patients were given an equal number of identical placebo capsules and PIPs measured. Records were evaluated by a scorer unaware of the patient drug studies. PIPs were recorded on a Grass 7P3A integrator preamplifier (Model 78) using galvanometers with a two inch deflection. The amplifier was set on its highest sensitivity with the lowest threshold and full rectification. The 1/2 low frequency time constant was at 10 and the integrator time constant on 0.02. Individual deflections were counted if they were at least twice baseline but not associated with spindles or within 10 seconds of movement artefact. Because PIPs often occur in bursts not all could be counted. To partially avoid the misleading idea that absolute numbers have a meaning, a ratio of counts per minute in NREM vs per minute in REM is presented.

In the two patients NREM/REM placebo PIPs were 0.083 and 0.2091 which

rose to 0.3207 and 0.8614 respectively after 2-3 weeks PCP treatment (2 gm/24 hr). This represented an approximately four-fold rise in the NREM-REM ratio for both patients at a time when REM sleep was 10-30 percent below baseline. This change was due both to a decrease in PIP counts in REM and an increase in NREM sleep. In addition to PCPA increasing PIP activity during NREM sleep, a large number of rapid eye movements during NREM (primarily stage II) were noted. This was usually but not always accompanied by a brief change in EEG (toward stage I) and a loss of muscle potential lasting 3-5 seconds.

These exploratory studies encourage further efforts to test the equivalence of PGOs and PIPs, as well as suggesting the great theoretical importance of searching for PIPs in the waking lives of hallucinating patients.

Significance to Mental Health Research:

Taken together with earlier work of this and other laboratories, the studies described draw a tighter net around the implication of brain monoamines in the mechanisms of sleep, and point to the possible relevance of stress and increased corticosteroid levels in disturbing those mechanisms. We believe, therefore, that they may be quite relevant to current thinking about disordered catecholamine in mental illness

Proposed Course of Project:

The issues raised by these studies are now being pursued in several directions. In collaboration with Dr. Robert Henkin of NIAMD sleep is being studied in Addisonian patients both in the presence and absence of their maintenance steroid medications.

In collaboration with Dr. William Orr of the Army Institute of Research at Walter Reed, an attempt is underway to investigate the effects upon sleep of stress experimentally produced by adversive conditioning procedures in Rhesus monkeys. We anticipate no problem in producing acute stress identifiable by elevated cortico steroid excretion, and hope to be able to produce long-term sustained stress in these animals. By this means we should be able to test whether acute physiological elevation of corticosteroids is accompanied by comparable sleep effects to those we have produced with prednisone in humans, and whether sustained steroid elevation results in the much more striking alterations of EEG sleep we have observed in severely depressed patients.

Publications:

Wyatt, R.J., Chase, T.N., Engelman, K., Scott, J., and Snyder, F.: Effect of L-dopa on the sleep of man. Nature 228: 999-1001, 1970

Wyatt, R.J., Engelman, K., Kupfer, D.J., Fram, D.H., Sjoerdsma, A., and

Snyder, F.: The effects of L-tryptophan (a natural sedative) on human sleep. Lancet 7678: 842-846, 1970

Wyatt, R.J., Engelman, K., Snyder, F., and Sjoerdsma, A.: Effects of 5-hydroxytryptophan on the sleep of normal human subjects. Electroenceph. clin. Neurophysiol. In press 1971

Wyatt, R.J., Chase, T.N., Kupfer, D.J., Scott, J., Snyder, F., Sjoerdsma, A., and Engelman, K.: Decreased brain catecholamines and human sleep. Nature In press 1971

Serial No. M-CP(C)-18-8
1. Laboratory of Clinical Psychobiology
2. Section on Clinical Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 20, 1971

Project Title: Psychophysiological Studies of Sleep and Waking in Normal Subjects

Previous Serial Number: None

Principal Investigator: Frederick Snyder

Other Investigators: Redford B. Williams, Jr., M.D., J. Christain Gillin, M.D., William C. Orr, Ph.D., Monte S. Buchsbaum, M.D., Adolf D. Pfefferbaum, Ph.D., Robert I. Henkin and Leonard S. Jacobs, M.D.

Cooperating Units: Laboratory of Psychology, Adult Psychiatry Branch, NIMH
Department of Experimental Psychophysiology, Walter Reed Army Institute of Research
Experimental Therapeutics, National Heart and Lung Institute, NIH

Man Years (1970):

Total:	3
Professional:	1 1/2
Other:	1 1/2

Project Description:

Objectives:

This heading encompasses a number of varied studies, most of them newly begun but all concerned with aspects of normal psychophysiology. One has to do with physiological changes related to direction of attention, whether outward or inward. A second tests the effects of total sleep and REM sleep deprivation on an intriguing rhythm of physiological and behavioral measures during waking, a cyclical pattern with a duration of 90 minutes, the usual duration of the REM sleep cycle. A third examines variations in auditory evoked potentials across the night of sleep. A fourth will extend existing data on the relationship between plasma growth hormone levels and stages of sleep to middle-aged and older subjects.

Rationales of each will be further elaborated together with their methods and findings.

Patient Material:

16 normal controls

Methods and Findings:

A. Psychophysiological Patterns in Relation to Direction of Attention

This area of work being carried forward by Dr. Redford Williams extends previous psychophysiological interest in the differential bodily changes concomitant with attention directed outward vs attention directed inward. Primarily it has utilized a strain gauge measure of forearm blood flow (FBF), but will now begin to employ an entire battery of surface physiological measures, including heart and respiratory rates, galvanic skin pontials, electromyogram, electroculogram, electroencephalogram and electrogastrogram. The typical protocol involves the simultaneous sampling of these measures during scheduled baseline periods and a variety of experimental conditions such as a word association test (WAT) or an interview about current life situations (INT).

In a pilot study recently completed all volunteers showed significant increases in FBF during intervals when their attention was directed inward by the WAT, while half of the subjects had significant decreases in FBF during the attention outward by INT. Those subjects who displayed just the opposite FBF response to INT appeared to be avoiding interaction with the interviewer. The challenge for future work is to simplify and better define the experimental conditions as well as to find means of objectifying subjects' individual responses to them. The significance of these studies stems from their bearing on the concept of 'physiological arousal,' so important in psychiatric thinking. If, indeed, arousal has both intensity and directional properties, then we must understand the latter in order to quantify the former.

B. Effects of Total and REM Sleep Deprivation on Physiological and Performance Rhythmicity

Recent research in the Department of Psychophysiology at the Walter Reed Army Institute of Research has shown very interesting relationships between long-term (11-22 hours) concomitant recordings of physiological (heart rate and rectal temperature) and behavioral measures. More specifically, through somewhat sophisticated data analytic techniques, it has been shown that regularly

occurring or periodic variability tends to be quite similar in physiological as well as behavioral measures. The behavioral measures were taken from the subject's performance on a complex signal detection task. Dependent measures were observing responses per 10 minute interval and the probability of signal detection per 10 minute interval.

This research has raised several interesting questions concerning the effects of sleep deprivation. In general, one day of sleep deprivation produced an effect on these rhythmic processes which was quite distinct from that found with a mild tranquizing agent. In very general terms the effect of the 24-hour sleep deprivation was to exaggerate the slower oscillations in the range of the circadian rhythm and to lessen the faster ones. Other results from this work have interesting implications for sleep research. Specifically, a 90 minute cycle has been found consistently in both physiological and behavioral parameters. This may be the first solid evidence indicating that the 90 minute REM-NREM cycle, so obvious during sleep, is actually the manifestation of a biological rhythm continuous throughout the diurnal cycle. We have undertaken, therefore, to collaborate with Dr. William Orr of A.I.R. in studying the effects of longer durations of sleep deprivation, specifically intervals of 36-48 hours, as well as effects of REM deprivation without total sleep deprivation. In the 90 minute waking cycle actually does relate to the 90 minute REM cycle, then we would expect the waking cycle to be accentuated after several nights of REM sleep deprivation. The first subjects are just about to be run in this study.

C. Auditory Evoked Potentials During Sleep

Previous work of Dr. Monte Buchsbaum and others has shown that certain normal persons tend to show exaggerated increases in evoked potentials to increasing intensity of auditory stimulus ('Augmenters') while others tend to dampen their responses at the higher intensities ('Reducers'). Collaborative studies with Dr. Buchsbaum examine changes in auditory evoked potentials (AEP) across the night of sleep looking for differential tendencies to augment or reduce inherent within the several EEG stages of sleep.

Following a night of adaptation to the sleep laboratory and the auditory clicks, AEP is automatically collected by computer, and averages obtained for the several EEG sleep stages across two or three nights. Completed data analysis from one subject

suggests a clear tendency for greater reducing of AEP in the progression from REM sleep through the successive planes of non-REM sleep (stages 2 to 4). Data from the remaining subjects is still being analyzed.

D. Growth Hormone Release During Sleep in Relation to Subject's Age

One of the more dramatic findings of recent sleep research has been that of an association between the high voltage slow wave stages of sleep (stages 3 and 4) and peaks of plasma growth hormone, a discovery with many likely implications for understanding the significance of slow wave sleep and considerable significance for relationships between sleep and development.

Thus far this work has been limited to the young adult subjects who happen to have large portions of slow wave sleep and might be expected to have high levels of growth hormone. By collaboration with Dr. Robert Henkin of the Experimental Therapeutics Branch, NHLI, we propose to study such relationships in middle-aged and older subjects, who typically have much less slow wave sleep as well as lower levels of plasma growth hormone.

There are special problems involved in obtaining normal volunteers beyond the young adult age range who are willing to spend a series of nights sleeping in our laboratory with catheters in their veins. So far a number have been found and the first study completed. That subject, a 40-year-old woman, had very little slow wave sleep and low growth hormone levels. It's hoped that a sufficient series of subjects can be studied to allow for correlation between these two measures and to permit the separation of sleep variables from the age variable itself.

Significance to Mental Health Research

Since normal relationships between behavioral and physiological variables must be understood before abnormal ones can be evaluated, the significance of these studies to mental health research is self evident.

Proposed Course:

All are studies newly undertaken and are expected to be completed within the next year.

Publications:

Snyder, F.: The phenomenology of dreaming. In Madow, L. and Snow, L.H. (eds.): The Psychodynamic Implications of the Physiological Studies on Dreams. Springfield, Ill., Charles C. Thomas, 1970, pp. 24-151.

Snyder, F.: Significance of ocular movements during dreaming activity. Presented at the Colloquium 'La Fonction du Regard,' Paris, May 1969. To be published in the proceedings, 1971, in press.

Snyder, F.: Psychophyiology of human sleep. Presented at the 20th Annual Meeting of the Congress of Neurogical Surgeons. To be published in the proceedings, in press.

Snyder, F. and Scott, J.: Psychophysiology of sleep. In Greenfield, N. and Sternbach, R. (eds.): Psychophysiology. New York: Holt, Rinehart and Winston, Inc., 1971, in press.

Serial No. M-CP(C)-18-69
1. Laboratory of Clinical Psychobiology
2. Section on Clinical Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Longitudinal Studies of Sleep and Concomitant Biological Changes in Psychiatric Patients

Previous Serial Number: Same

Principal Investigator: Frederick Snyder, M.D.

Other Investigators: David H. Fram, M.D., Richard J. Wyatt, M.D., J. Christian Gillin, M.D., Leonard S. Jacobs, M.D., Redford B. Williams, Jr., M.D., Bernard L. Frankel, M.D.

Cooperating Units: Section on Psychiatry, CBRS, NIMH
Laboratory of Clinical Psychopharmacology, SMR, NIMH

Man Years (1970):

Total:	4
Professional:	2
Other:	2

Project Description:

Objectives:

The broad purpose of this project is that of seeking objective correlates of mental illness which will provide quantifiable assessment of clinical course and effectiveness of therapeutic efforts over a broad spectrum of diagnostic entities. Although other measures are being explored, the primary focus continues to be the longitudinal study of electrographic sleep patterns and their changes in relation to changes in the clinical status of individual patients. To that end, an inpatient program has been underway in which selected patients are intensively treated by a variety of appropriate means, while behavioral ratings, all-night sleep patterns, and other biological measures are obtained on a serial basis.

In this manner the project has so far delineated two very striking and distinctive patterns of sleep derangement in the important psychiatric situations of psychotic depression and acute schizophrenic psychosis. Present efforts are devoted to further evaluation of the possible significance of these changes, and to the search for comparable alterations in other conditions.

Methods Employed:

EEG, eye movement and chin muscle potentials are continuously recorded over entire nights from patients sleeping in their own beds on a specially equipped psychiatric ward. This is done on a longitudinal basis as long as the particular patient's clinical status is of research interest, and individual case studies have ranged from 36 to 200 or more nights. Electrographic records are scored without knowledge of their sequence in relation to changes in clinical course, as that is assessed by daily clinical ratings on various dimensions of behavior and psychopathology made by the nursing staff. Other biological measures, such as waking forearm blood flow, are obtained concomitantly.

Aside from the attempt to maintain patients without drugs for approximately one month of baseline evaluation, ordinarily their treatment is determined by individual clinical considerations. Since considerable data has accumulated by now with regard to the effects upon sleep of the drug treatments routinely used, this becomes an increasingly important subject of research in itself. Such evaluations have concentrated upon two agents used in the treatment of depression, the monoamine oxidase inhibitor 'Nardil.' and amitriptyline HCI, 'Elavil.' as well as the oldest and most commonly used tranquilizing agent, chlorpromazine.

Finally, in certain cases efforts have been made to alter sleep patterns and to look for possible effects in waking behavior or to test certain theoretical questions about abnormalities of sleep in mental illness.

Patient Material:

33 psychiatric patients

Major Findings:

Many of the specific studies described under this heading last year have been completed and are either published or awaiting publication. Data collection for the longitudinal studies of depressed and schizophrenic patients has continued during the past year, but is now coming to a close. Of the vast amount of sleep recording collected for that purpose over the past four years, much has been scored and analyzed while much more still remains to be processed. Final conclusions must await the completion of that laborious task. In the meantime, the following studies have been undertaken during the past year.

A. Experimental REM Deprivation

We have previously reported that episodes of acute schizophrenic psychosis are accompanied by varying degrees of total sleep disturbance and disproportionately reduced REM sleep. We noted in these naturalistic studies that there was little or no evidence of compensatory REM increase following such episodes, unlike the marked REM rebounds we have seen in depressed patients, while Zarcone and Dement at Stanford University have described a lack of REM compensation after experimental deprivation in actively ill schizophrenics. Since these findings are complementary and suggest something unusual about schizophrenic sleep, we have replicated the Stanford study in both psychotic and non-psychotic patients.

Six actively ill schizophrenics (the AS group mean age 25.8) and five non-psychotic patients (the NP group, mean age 23.8) were partially REM deprived by the awakening method for two consecutive nights. None of the patients had been treated with psychotropic medications for at least a month prior to the baseline period.

During the baseline period (4-10 days, mean = 6), the NP group had significantly more REM sleep than the AS group (99.7 vs 86.3 min., $p < .03$, Mann-Whitney U Test, two-tailed) though NREM times were similar (NP 279.4 $\pm$ 52.0 vs 301.4 $\pm$ 33.1). Over the two deprivation nights the AS group averaged 24 minutes REM/night, the NP group 28 minutes REM/night, thus representing a loss of 71.2% and 71.9% of baseline RT respectfully.

During the five day recovery period, the NP group had a significant REM rebound (comparing the last four days of baseline with the 5 recovery days, based on minute RT/night, $p < .01$, Friedman two-way analysis of variance, one-tailed test, $X_r = 18.17$, $df = 8$), the AS group did not ($p < .25$, $X_r = 7.46$, $df = 8$). Based on percent of baseline RT in minutes, the rebound for the NP group over the 5 recovery days is significant at $p < .01$ ($X_r = 12.64$, $df = 4$) but the AS is not ($p < .40$, $X_r = 2.00$, $df = 4$). There was a suggestion of a small delayed rebound on R_3 for AS.

Though the data support the Stanford finding that actively ill schizophrenic patients fail to rebound, it must be stressed that there was considerable variability within the AS group, some psychotic patients had clear-cut REM rebounds and one of the non-psychotics did not. Hence our present guess would be that failure of REM rebound after experimental deprivation is not a specific feature of schizophrenic psychosis but more likely is something like a general indication of prevailing anxiety or stress.

B. Longitudinal Studies of Waking Psychophysiology

Somewhat belatedly we have undertaken a program of studying measures of waking psychophysiology in the same longitudinal fashion we have been studying sleep in order to look for relationships between the two. Although it is intended that this will soon include a considerable battery of measures, thus far it has been limited to one, forearm blood flow (FBF) reputed to be a correlate of anxiety or arousal. Two patients, one schizophrenic and the other manic have had FBF measurements made on a daily basis, each over several months. While the results have not yet been correlated with sleep data, they have been compared with changes in clinical state.

The schizophrenic patient showed a gradual increase in FBF during the initial weeks after admission coinciding with progressive behavioral deterioration. Then while the patient remained in a state of overt psychosis and disorganization FBF remained in a middle range, rising again to a striking peak coincident with the beginning of behavioral improvement. The manic patient showed a sharp decrease in FBF about 24-hours before the acute onset of a full-blown manic episode. The FBF remained low during the first half of the episode, then gradually increased to a peak just at the time when mania began to subside.

Although no conclusions can be drawn from these two patients, results do suggest there is more than random correlation between this peripheral physiological measure and important developments in the natural histories of mental illness. Circumstances permitting, efforts will be made to study many additional patients in the same manner together with a variety of other psychophysiological measures.

Significance to Mental Health Research:

Until very recently little systematic evidence about the nature or degree of sleep disturbance in relation to various categories of psychiatric illness has existed. Thus far the present project consitutes the most extensive and intensive effort made to obtain such information. We believe it proves the value of EEG sleep profiles as objective indicators of changing clinical status, permitting additional delineation of the natural histories of illness as well as of the effectiveness of therapeutic interventions. At the same time, it provides the opportunity for testing specific hypotheses about possible causal relationships of varying kinds of sleep disruption to disturbances of waking behavior.

Proposed Course of Project:

While additional sleep and waking data will be collected on highly selected patients, the extensive efforts carried out on inpatients over the past four years will be brough to a close. Although many issues remain, the exhaustive naturalistic approach we have pursued had reached a point of diminishing returns. Data collection far outstripped our capacities for data processing, and the particular kinds of patients we needed to delve further had become increasingly scarce among our referrals.

Two new directions of exploration are the natural outgrowths of our past work. The one would involve studies of sleep in less disturbed patients such as chronic anxiety neurotics and insomniacs. Information about their sleep is needed to put our findings about sleep of the severely ill in perspective. Hopefully such information can be obtained on an outpatient basis by employing a telephone link to provide EEG sleep records while the patients remain in their own homes.

The second direction, already begun, will involve examining the consequences for sleep of experimental stress in monkeys. If it should prove possible by that means to duplicate the abnormalities of sleep we have found in certain patients, then we would be in a much better position to evaluate the neurophysiological and biochemical significance of those abnormalities.

Publications:

Kupfer, D.J., Meltzer, H.Y., Wyatt, R.J. and Snyder, F.: Serum enzyme changes in sleep deprivation. Nature 228: 768-770, 1970.

Kupfer, D.J., Wyatt, R.J., Greenspan, K. and Snyder, F.: Lithium carbonate and sleep in affective illness. Arch. Gen. Psychiat., 23: 35-40, 1970.

Kupfer, D.J., Wyatt, R.J. and Snyder, F.: Comparison between electroencephalographic and systematic nursing observations of sleep in psychitric patients. J. Nerv. Ment. Dis., 151: 361-368, 1970.

Kupfer, D.J., Wyatt, R., Snyder, F. and Davis, J.M.: Chlorpromazine and sleep in psychiatric patients. Arch. Gen. Psychiat., 24: 185-189, 1971.

Snyder, F.: NIH studies of EEG sleep in affective illness. In Recent Advances in the Psychobiology of Depressive Illnesses. Washington, D.C.: Public Health Service, U.S. Government Printing Office, 1971, in press.

Wyatt, R., Fram, D.H., Kupfer, D.J. and Snyder, F.: Total prolonged drug-induced REM sleep suppression in anxious-depressed patients. Arch. Gen. Psychiat., 24: 145-155, 1971.

Wyatt, R., Portnoy, B., Kupfer, D.J., Snyder, F. and Engelman, K.: Resting plasma catecholamine concentration in patients with depression and anxiety. Arch. Gen. Psychiat., 24: 65-70, 1971.

Serial No. M-CP(C)-18-6
1. Laboratory of Clinical Psychobiology
2. Section on Comparative Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Comparative Studies of Sleep

Previous Serial Number: Same

Principal Investigator: Frederick Snyder, M.D.

Other Investigators: Thomas C. Douthitt, Ph.D. and Nellie Bugbee

Cooperating Units: Section on Technical Development, IRPD, NIMH
Laboratory of Neurophysiology, BBR, NIMH
National Zoological Park

Man Years (1970):

Total:	3
Professional:	1 1/2
Other:	1 1/2

Project Description:

Objectives:

The general objective of this project is to explore the phylogenetic manifestations and adaptive function or functions of sleep by systematic comparative study of that phenomenon in a broad variety of animal forms and under varied environmental conditions. The first phase of the project has been largely methodological, the development of telemetric techniques for the recording of electrophysiological activity from unrestrained animals in large enclosures and over extended periods of time. This involved the design, manufacture and testing of special micro-miniature radio transmitters suitable for implantation into small animals, as well as development of appropriate receiver systems to capture their signals. While certain methodological refinements are still being pursued, a usable system was achieved during the past year and data collection is now well underway.

Methods Employed and Major Findings:

A. Technical Aspects

1) Packaging for implantation - A working solution has been found for the difficult problem of sealing telemetry transmitter and battery against body fluids. Each is separately sealed by a thin coating of a mixture consisting of four parts paraffin and one part a plastic substance called Elvox. In effect this produces a tough, pliable wax coating not subject to the ready cracking of paraffin alone. Quite consitently this packaging maintains the integrity of the implanted system over the intervals of two or three months while the battery lasts.

2) Separation of Signals - Since the zone of FM broadcasting frequencies free of radio stations is quite narrow, monitoring separate signals from more than one animal under simultaneous study becomes a frustrating problem. This has been satisfactorily solved by individually screening each observation box and receiving antenna with copper mesh. By this means it is now possible to record from eight animals at one time even if the transmitting frequency of all are very close together.

3) Antenna System for Outdoor Enclosure - In order to use the same telemetry system for recording in our large outdoor enclosure on the grounds of the National Zoological Park, it has been necessary to devise a system of sixteen antenna arrays together with a switching system to select that antenna element receiving the strongest signal. This has been a challenge successfully met by Mr. James Bryan and the Section on Technical Development during the past year, so that we are now ready to begin data collection at the zoo facility.

The approaches described here and in the previous annual report provide us with a miniature telemetry system capable of broadcasting EEG or other physiological signals over a radius of 20 ft. with a single antenna array, or multiples of 20 ft. with the more complex antenna system. The sealed transmitter itself weighs less than one gram and is small enough to be totally implanted on the head of a rat. Battery weight remains the limiting factor determining duration of undisturbed recording, but with battery packages weighing 10 grams we obtain continuous transmission from two to three months. Further work is in progress to incorporate miniature magnetic latching switches, so that battery life may be extended by turning the transmitter on and

off remotely. As a further improvement efforts are underway to incorporate microminiature preamplifiers within the transmitters to improve the signal to noise ratios.

B. Phylogenetic Studies

Data has been collected so far from small numbers of animals of several species over extended series of twenty-four hour samples. Emphasis has been given to comparisons among primitive mammals studied under standard conditions, with some beginnings at studying the same animals under systematically varied conditions.

Sleep in Primitive Mammals - After ten days recovery from the surgery involved in implanting transmitter and battery, each animal is placed in a screened and sound shielded 64 cubic ft. recording unit containing an appropriate nest box or hollow log. perches, etc. Temperature is kept more or less constant, an artificial light cycle of 12-hours light and 12-hours darkness is maintained within each enclosure, and animals are fed at the same time each day. Without further disturbance to the animals baseline recording is obtained over twenty-four hour periods two or more days each week for at least one month prior to any experimental intervention. Records are scored and recorded by hand and the data analyzed and graphed by computer.

In this fashion comparisons have been made during the past year among the marsupial, Didelphis marsupialis, two insectivores, Centetes ecaudatus and Erinaceus europaeus, and the primitive rodent, Aplodontia rufa. Didelphis remains the champion sleeper, averaging 63% of twenty-four hour sampling time in sleep, 27% of which is REM sleep. Both figures are somewhat lower than we had found in ourmuch earlier studies by the cable method or those found in a recent study at Yale University, but the number of our specimens is still small and there are individual variations. The two insectivores are highly similar to one another in terms of the total fraction occupied by sleep (about 45% of the twenty-four hour period), but surprisingly discrepant in the portion of sleep occupied by REM. For Erinaceus REM has averaged 35%, while for the tenrec, Centetes, the mean has been 18%. Aplodontia, the only strict vegetarian among these forms, displays a highly polycyclical pattern of sleep and waking with a total sleep fraction of 45% of which 23% is REM.

There are already indications that the usual characterizations of animals as nocturnal or diurnal is simplistic. On our standard artificial light cycle of 12-hours dark and 12-hours light none of the species so far studies sleeps in one or the other phase exclusively. The hedgehogs have shown the clearest relationship, with sleep predominating during and coextensive with the light phase and waking throughout the dark phase. Yet the tenrec shows only slightly more sleep interspersed during the dark than during light. The small amount of time the native opossum spends awake is mainly in the dark, but Aplodontia shows no discrimination between light and dark periods at all. Rather, that curious little animal exhibits an extremely regular alteration between sleep and waking with a highly consistent frequency of 5 to 6 cycles a day.

It is impressive that sleep is so prominent in the lives of all of these primitive mammals and that REM sleep is a clearly defined aspect in each form. Yet there are consistent differences in the typical amount and patterning of sleep which are not obviously related to phylogenetic relationships. Extremes of 18% and 35% in REM proportion occur in the two most closely related forms we have studied, Erinaceus and Centetes. From such data as well as from similar indications in the work of others, it now appears most probable that the wide species variations in patterning of mammalian sleep reflect quite specialized adaptations of these species rather than any broader phylogenetic principles. Generalizations about the significance of these variations must await information about many more forms.

C. Experimental Modifications of Sleep

The second aspect of our interest in this area is to examine just how the typical twenty-four hour patterning of sleep and waking in various species is affected by altered external and internal conditions. The most important methodological question is how sleep patterns differ when recorded by our telemetry method than when recorded by a hard wire cable attached to the animal. We have made some small scale comparisons in opossums and hedgehogs, finding minor but inconsistent differences. With the cable method opossums have slept about 10% less with slightly disproportionate loss of REM, but hedgehogs have actually slept 4% more without alteration of REM. Since both are excellent sleepers, we would expect much larger differences in tenuous sleepers such as rabbits or ungulates, but these remain to be studied. Whether or not the cable method itself effects sleep, it poses serious limitations on the conditions under which

animals can be studied. With cables attached their movement is restricted and they must be alone in an empty enclosure. The telemetry technique permits complete mobility, social interaction with other animals and freedom to seclude in nest boxes, etc. First efforts are being devoted to the effects of such variables, but there is an almost limitless list of conditions which should be tested eventually.

Significance to Mental Health Research:

The instrumentation so far provided by this project promises to have wide application in the study of animal physiology and behavior. For the first time this type of instrumentation permits us to make physiological assessment in relation to really free and natural behavior. As applied to the specific focus of this project, the comparative study of sleep, hopefully it will enable us to contribute to basic biological understanding of that vital phenomenon.

Proposed Course of Project:

In addition to extending the data collection for the animals currently under study, collection of similar data from commonly used laboratory animals such as cat, guinea pig, domestic rabbit and albino rat will have high priority. Additional primitives, such as the Australian echidna, Tachyglossus aculeatus, four-eyed and wooly opossums, Metachirus nudicudatus and Caluromys, and brush tailed phalangers, Trichosurus vulpecula, will be studied as soon as time permits. A similar approach will be extended to more natural conditions at the National Zoo enclosure and at the Poolesville ungulate facility.

Publications: None

Serial No. M-CP(C)-18-7
1. Laboratory of Clinical Psychobiology
2. Section on Comparative Studies
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Factors affecting intraspecific and predatory aggression in the rat

Previous Serial Number: None

Principal Investigator: Burr. S. Eichelman, Jr., M.D., Ph.D.

Other Investigators: Redford B. Williams, Jr., M.D., Wybren De Jong, M.D., Ph.D., Nguyen Bich Thoa, Ph.D. and Larry Ng, M.D.

Cooperating Units: Experimental Therapeutics Branch, National Heart and Lung Institute, NIH
Office of the Chief, Laboratory of Clinical Science, NIMH
Section on Experimental Therapeutics, Laboratory of Clinical Science, NIMH

Man Years (1970):

Total:	1.7
Professional:	1.4
Other:	.3

Project Description:

Objectives:

This project is designed to provide an overview of aggressive behavior in the rat, an overview encompassing strain characteristics and types of aggressive behavior, as well as their pharmacology and neuroanatomical correlates. The information from these studies is also being contrasted with mouse aggression.

Methods Employed:

The studies center around three behavioral tests: shock-induced aggression, jump-flinch thresholds to pain, and mouse-killing behavior. The first two paradigms have already proved fruitful as areas of research in delineating aggressive behavior (Eichelman, B.: J. Comp. Physiol. Psychol. 74:331-339, 1971). Ancillary techniques employed utilize cannula and intracisternal application of pharmacologically active drugs, surgical excision or lesioning, monitoring of blood pressure (rat tail), and monoamine or related enzyme measurements.

Sub-projects:

1) Strain Variability - The experimental paradigms of shock-induced aggression and mouse-killing are being studied in relation to strain differences in rats. There is a significant variation in aggression as well as in the response to footshock. Osborne Mendel rats (NIH) demonstrate a group probability of 0.5 for mouse-killing and shock-induced fighting constrasted with NIH Wistar which do not show mouse-killing, but fight at 0.5 or Sprague Dawley rats which have a killing probability of 0.1 and fight 0.2. As suggested by the Wistar strain studied, there is no correlation between high fighting pairs in the shock-induced paradigm and the predatory behavior of mouse-killing either within or between strains. However, the strain differences strongly point to genetic differences meriting further study.

Strain variability has been previously noted in isolation-induced aggression in mice. This laboratory in collaboration with Dr. B. Slotnick has been attempting to develop an electrical circuit capable of monitoring and distinguishing mouse-fighting over prolonged periods up to one week. Once this system is perfected, long-term studies of brain lesions and drugs will be initiated.

2) Sensory Input - The role of sensory input and its effect on aggression and pain threshold is being studied in collaboration with Miss Nellie Bugbee. Total olfactory bulbectomy in the rat induces mouse-killing behavior. This has been validated in our laboratory, however, there is no change in intraspecific shock-induced aggression. Bulbectomy does lower the rat's jump threshold to electric shock, demonstrating that an interruption of one sensory input changes the behavior response to another sensory stimulus. Removal of rat vibrissae substantially decreases shock-induced fighting, while blinding and decreasing hearing produces no change in shock-induced or predatory aggression.

3) Experimental Manipulations - Hunger and prolonged swimming stress do not alter fighting. Sleep deprivation and/or immobilization increases fighting. REM deprivation and/or greater immobilization increases it further. Experiments are underway evaluating the role of immobilization and its relation to this form of aggression. Also, we are pharmacologically manipulating the sleep cycle of rats with MAO inhibitors and pCPA. PCPA has a statistically, but probably not behaviorally significant increase in shock-induced fighting. It does conversely have a profound effect in initiating mouse-killing behavior and the lowering of pain thresholds. To relate fighting behavior to EEG sleep patterns subsequent groups of rats treated, as cited above, will be monitored with wire or transmitter recording to evaluate their sleep cycles.

4) Pharmacological Manipulations - Another approach with Dr's Ng and Thoa has been intracisternal drug injections. We have found a five-fold increase in shock-induced fighting with the cisternal injection of 6-hydroxydopamine. Following the completion of the behavior studies of these animals assays of CNS norepinephrine and serotonin will be done, as well as evaluation of adrenal enzymes.

A substantial portion of this year has been spent in the development of cannulae placement for the study of topically placed neuro-active substances into the CNS followed by the observation of fighting, predatory behavior, and pain thresholds. At present the preliminary results show a raising of the pain threshold with cholinergic stimulation of the ventromedial nucleus of the hypothalamus. There was no change in jump thresholds with norepinephrine. Neither NE or carbachol produced significant changes in fighting behavior or mouse-killing. This study is being expanded to include other drugs as well as other anatomical locations.

5) Hypertension - In studying strain differences among rats, we have looked at hypertensive strains: the Okamoto SHR, Dahl's strains of inducible hypertensives, and Wistar rats made hypertensive by renal artery clamping. A larger sample of the Dahl strains have yet to be studied, however SHR females are markedly less aggressive than Wistar females. This is not inseparably linked to the hypertensive character, however, as matched Sprague Dawley females are also quite pacific, yet normotensive. It appears that decreased aggression may have been co-selected with the character of hypertension. This same trend has been noted in a small number of rats already studied in the Dahl strains. Hypertension per se, however, has no detectable change on shock-induced fighting since

hypertensive rats produced by renal artery clamping are inseparable from controls in terms of fighting and jump thresholds. Genetically hypertensive rats also tend to have higher jump thresholds than matched normotensives.

While studying normal blood pressure changes in Osborne Mendel rats we have found a differential response in blood pressure and pulse following shock-induced fighting, vs the presentation of the same shock intensity and number to the rat alone in an escape paradigm. Following fighting, there is a mean drop in tail blood pressure (capillary filling) of 15mm which apparently lasts less than two hours. Conversely, following isolated escape there is a 20mm rise in pressure. We are initiating with Dr. D. Henry catecholamine collections under these two conditions to begin a study of this differential response.

A collaborative study to be undertaken during the remainder of this year with Dr's Cardon and Watanabe involves the placement of cannulae into the rat hypothalamus to evaluate the presumed effect of Dopa or its metabolities on a CNS hypotensive effect.

Significance to Bio-medical Research and the Program of the Institute

Intraspecies aggression in the rat is a distinct form of aggression from predatory mouse-killing behavior. Both appear to be genetically linked and vary from strain to strain. Both forms of behavior respond differently to brain lesions (bulbectomy) and drugs (pCPA). The propensity for hypertension may be co-selected with decreased aggression and decreased response to pain. Monoamine such as dopamine and norepinephrine appear to be related to intraspecies aggression more significantly than serotonin, which in turn appears more related to predatory behavior and pain thresholds. External factors such as the disruption of sleep may alter aggressive behavior. As yet we do not know if it may be achieved through an initial alteration of a monoamine system.

Proposed Course of Project:

The completion and further extension of those sub-projects as listed above.

Publications: None

Serial No. M-CP(C)-18-5
1. Laboratory of Clinical Psychobiology
2. Section on Psychophysiology of Sleep
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Factors Affecting Proportion of REM sleep

Previous Serial Number: Same

Principal Investigators: Frederick Snyder, M.D., Jimmy Scott, Ph.D. and Miriam F. Kelty, Ph.D.

Other Investigators: None

Cooperating Units: None

Project Description:

Objectives:

Data collection for this study was completed and the project discontinued after Dr. Scott and Dr. Kelty left the Laboratory.

Serial No. M-CP(C)-18-18
1. Laboratory of Clinical Psychobiology
2. Section on Psychophysiology of Sleep
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Sleep Stages in Relation to Critical Reactivity After Abrupt Awakenings

Previous Serial Number: Same

Principal Investigator: Jimmy Scott, Ph.D.

Other Investigators: Frederick Snyder, M.D.

Cooperating Units: None

Man Years (1970)

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives:

Project is discontinued. Data collection was complete before Dr. Scott left NIMH, but we are still awaiting his completion of its analysis and reporting of results.

Serial No. M-CS-OC(C)-04
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies of the interrelationships of the nervous and circulatory systems

Previous Serial Number: Same

Principal Investigator: Philippe V. Cardon

Other Investigators: August M. Watanabe, James L. Weiss, Thomas N. Chase, Irwin J. Kopin, Louis Lemberger, W. Stephen Brimijoin and Cal K. Cohn

Cooperating Units: Sections on Pharmacology, Experimental Therapeutics and Medicine, LCS

Man Years:

Total	1.75
Professional	1.75
Other	None

Project Description:

Objectives: To study the interaction of the nervous and circulatory systems and the effects of drugs on those systems.

Methods Employed: Standard nontraumatic techniques for assessing well-known circulatory parameters in man. Direct measurement of analogous parameters in animals. Electrical recording of peripheral sympathetic nerve activity in animals.

Major Findings: (1) The occurrence of cardiac arrhythmias in patients receiving therapeutic amounts of ℓ-dopa was documented as was absence of arrhythmias when the therapeutic dose of ℓ-dopa was reduced as a result of concurrent administration of a peripheral inhibitor of dopa-decarboxylase.

Three major findings in animals have extended and strengthened the evidence that the hypotensive effect of ℓ-dopa is due primarily to the central action of some decarboxylated product of ℓ-dopa. (a) It was shown biochemically that the effects of peripheral and central inhibitors of dopa-decarboxylase administered to dogs in the doses used in studies described last year are as was postulated: Decarboxylase was inhibited only in the periphery by one of the agents employed and both centrally and peripherally by the other agent. (b) When given to cats pretreated with a peripheral decarboxylase inhibitor, ℓ-dopa markedly reduces the electrically recorded activity of postganglionic (renal and cardiac) and preganglionic (cervical) sympathetic nerves. The reduction is closely related

in time to the reduction in blood pressure and to cardiac slowing. (c) Ganglionic block or end-organ unresponsiveness must be minor contributors to the circulatory effects if indeed they occur at all. The earliest noticeable effect of postganglionic nerve activity is reduction of the duration rather than of the amplitude of the activity bursts; response of the nictitating membrane to preganglionic nerve stimulation is nearly normal (the possibility of slight quantitative reduction being still open).

Blood catechol-O-methyltransferase in patients with parkinsonism has been measured. Levels are similar to normal levels in the control state but decrease significantly when therapeutic doses of ℓ-dopa with or without a peripheral decarboxylase inhibitor are administered. The reason for this phenomenon is not known.

(2) Circulatory effects of tetrahydrocannabinol (the major active constituent of marihuana) have been assessed in a double-blind study involving marihuana users. The planned study of ten subjects will be complete by the end of the fiscal year. Preliminary results show a consistent abolition of reflex veno-constriction following a deep breath, tachycardia as described by others and possibly greater forearm arteriolar constriction in response to vertical tilt. As part of the same study, data on the metabolism of orally administered tetrahydrocannabinol have been obtained.

(3) Effects of 6-hydroxydopamine, a destroyer of sympathetic nerve endings, on ganglionic transmission were studied. Shocks applied to the greater splanchnic nerve were recorded from the splenic nerves of rats. The hypothesis that damage to the nerve endings would result in impaired ganglionic transmission was not confirmed since normal transmission was demonstrable at all time periods studied after administration of the agent.

Significance to Biomedical Research and the Program of the Institute: A thorough understanding of the effects of ℓ-dopa and tetrahydrocannabinol is essential for their rational use or control.

Proposed Course of Project: Investigation of the sites of action and the nature of the active metabolite(s) of ℓ-dopa by means of stereotactic insertion of dopamine and norepinephrine into likely areas of rat brains will be continued. Tetrahydrocannabinol and catechol-O-methyltransferase findings will be followed up.

Honors and Awards: None

Publications:

Cardon, P.V. and Guggenheim, F.G.: Effects of large variations in diet on free catecholamines and their metabolites in urine. *J. Psychiat. Res.* 7:263-273, 1970.

Prindle, K.H., Jr., Gold, H.K., Cardon, P.V. and Epstein, S.E.: Effects of psychopharmacologic agents on myocardial contractility. *J. Pharmacol. Exp. Ther.* 173:133-137, 1970.

Parks, L.C., Watanabe, A.M. and Kopin, I.J.: Prevention or reversal of levodopa-induced cardiac arrhythmias by decarboxylase inhibitors. *Lancet* 2: 1014-1016, 1970.

Watanabe, A.M., Chase, T.N. and Cardon, P.V.: Effect of ℓ-dopa alone and in combination with an extracerebral decarboxylase inhibitor on blood pressure and some cardiovascular reflexes. *Clin. Pharmacol. Ther.* 11:740-746, 1970.

Serial No. M-CS-OC(C)-13
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Medical and physiological investigations in major psychiatric illness

Previous Serial Number: Same

Principal Investigator: Philippe V. Cardon

Other Investigators: James L. Weiss and Peter S. Mueller

Cooperating Unit: Department of Psychiatry, Yale University (New Haven)

Man Years:		
	Total	0.25
	Professional	0.25
	Other	None

Project Description:

Objective: To define the effects of epinephrine on carbohydrate metabolism when administered in quantities similar to those likely to be secreted during severe depression.

Methods Employed: Urinary epinephrine and cyclic-AMP and blood glucose, insulin, growth hormone and free fatty acids are measured by standard chemical methods.

Major Findings: Epinephrine was administered intravenously to six normal volunteers in a double-blind design in doses of 0.1 and 0.3 μg per minute, and a standard intravenous tolerance test was carried during the infusions. As anticipated, these relatively small doses resulted in roughly two- and fivefold increases in the rate of urinary excretion of epinephrine--increases as large as those likely to occur in severe depression over a sustained period. No effect on glucose metabolism could be demonstrated. Results of other blood constituents measured are not yet available.

Significance to Biomedical Research and the Program of the Institute: Impaired glucose tolerance and increased epinephrine excretion in depression have been reported by several laboratories. Relatively large doses of epinephrine are known to impair glucose tolerance. The present findings suggest that the impaired glucose tolerance seen in depression is probably not the result of increased adrenal medullary secretion of epinephrine.

Proposed Course of Project: The project will be inactivated for at least one year.

Honors and Awards: None

Publications:

Berens, S.C., Bernstein, R.S., Robbins, J. and Wolff, J.: Antithyroid effects of lithium. *J. Clin. Invest.* 49:1357-1367, 1970.

Berens, S.C., Wolff, J. and Murphy, D.L.: Lithium concentration by the thyroid. *Endocrinology* 87:1085-1087, 1970.

Wolff, J., Berens, S.C. and Jones, A.B.: Inhibition of thyrotropin-stimulated adenyl cyclase activity of beef thyroid membranes by low concentration of lithium ion. *Biochem. Biophys. Res. Communic.* 39:77-82, 1970.

Serial No. M-CS-OC(C)-16
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies of pinched-off nerve endings (synaptosomes) as a model system for investigating the transport, binding and metabolism of monoamines

Previous Serial Number: Same

Prinicpal Investigator: Robert W. Colburn

Other Investigators: L. Keng-Yong Ng (Guest Worker), K.S. Rajan and Irwin J. Kopin

Cooperating Units: Section on Experimental Therapeutics, LCS and Illinois Institute of Technology Research Institute (Chicago)

Man Years: Total 1.0
Professional 1.0
Other None

Project Description:

Objectives: Synaptosomes isolated from whole brain represent an *in vitro* system similar in many respects to that present in living organisms. Current basic problems being investigated with this system are: (1) How do neurotransmitters pass through membranes? (2) How are they bound within vesicles? and (3) What is the mechanism for their release? A concurrent study involves investigation of the effects of psychotomimetic drugs on the above parameters for neurotransmitter substances.

Methods Employed: Optimal ionic, pH and substrate conditions for the functioning of synaptosomes were developed. Antidepressant drugs such as desmethylimipramine or antimanic drugs such as lithium are added to the synaptosome system; and the uptake, binding and release of a variety of neurotransmitter substances are measured. The chelating chemistry of neurotransmitters as a possible mechanism for binding and release in synaptosomes is studied.

Major Findings: The synaptosomes take up, bind and release monoamines such as norepinephrine and serotonin much as they function in *in vivo* or in perfusion experiments. The uptake is saturable, and kinetic findings such as Vmax and Km fit closely those found with other systems. Lineweaver-Burk plots indicate that many drugs act competitively in blocking net uptake of the amines. Chronic lithium treatment increases net uptake of monoamines when given at levels used clinically for mania. Uptake studies with neurotransmitters are of

importance since reuptake is a major means for termination. Recent findings with this *in vitro* synaptosome system provide evidence that dopamine administered at high doses displaces endogenous serotonin from its storage sites.

Significance to Biomedical Research and the Program of the Institute: The drugs altering monoamine function have proved very useful in modifying mood. The present studies provide information on a molecular basis concerning drug action.

Proposed Course of Project: With the above system large numbers of very similar samples can be prepared, and these will be used in comparing a wide variety of drugs using kinetic methods to determine active mechanisms. Synaptosomes will be further fractionated to isolate possible carrier or receptor proteins.

Honors and Awards: None

Publications:

Rajan, K.S., Davis, J.M. and Colburn, R.W.: Metal chelates in the storage and transport of neurotransmitters: Interactions of metal ions with biogenic amines. *J. Neurochem.* 18:345-364, 1971.

Serial No. M-CS-OC(C)-17
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biomedical application of gas chromatography/mass spectrometry to mental health problems

Previous Serial Number: Same

Principal Investigator: Theodore A. Walter (Guest Worker)

Other Investigators: Robert W. Colburn, Irwin J. Kopin and Henry M. Fales

Cooperating Unit: Laboratory of Chemistry, NHLI

Man Years: Total 1.0
Professional 1.0
Other None

Project Description:

Objectives: In the present study an intense examination is being made of the general metabolic patterns of depressed, manic and schizophrenic patients. Moreover, the manner in which such patients metabolize drugs like phenothiazines, for example, and the way they metabolize the compounds which accumulate with drug treatment are being studied. Particular emphasis is placed on neurotransmitter substances and their metabolic products and on whether the results observed reflect metabolism in the central nervous system or in the peripheral nerves.

Methods Employed: Two tools which have been recently developed are used for these studies. The first is a gas chromatograph with an automatic injection system. It allows for a rapid qualitative and quantitative survey of a very wide variety of metabolic intermediates. Such patterns of intermediates are compared between patients on the same ward eating the same diet or daily for one patient during normal periods and a psychotic manic or depressed period. The second prinicpal tool used is a combined gas chromatograph/mass spectrometer. When new intermediates are observed by the above screening technique with or without drug treatment, additional aliquots of the isolated sample are injected into the instrument. As the new unknown compounds pass out of the chromatographic column they are directed through an electron beam and split into ion fragements which are accelerated and passed through a magnetic field for separation and identification.

From this analysis a reasonable hypothesis may be made in most cases of the structure of the unknown compound. It is therefore a new rapid method for

identifying metabolic intermediates even with only a transitory isolation. In addition, following identification or partial identification with the technique, ion fragments may be selected which will give extraordinary sensitivity and specificity for assay of unknown compounds.

Major Findings: The findings to date have been limited but encouraging. The pattern of metabolites found in the urine of a given patient, for example, was found to be relatively constant over time; and it does not merely reflect the dietary intake for at least a great majority of the compounds measured. In the urine of one depressed patient a compound which was not present in urine of other patients on the same diet persisted. It was found to be a methoxybenzoyl conjugate of glycine by the methods described above. Chromatographic patterns of urine obtained from a patient before, during and after a psychotic event revealed unique chromatographic peaks which are currently under investigation. Studies of neurotransmitter substances by the above methods require that the methods be used at maximum sensitivity. Adequate sensitivity of the gas chromatograph/mass spectrometer has been achieved: Amounts as small as a few tenths of a nanogram of a metabolite have been detected. Other biological tissues which have been examined by these methods include blood, brain and cerebrospinal fluid, all of which give distinct chromatographic patterns for analysis; and peaks of the order of 300 to 400 have been isolated for study.

Significance to Biomedical Research and the Program of the Institute: Analysis of the biochemical pathways functioning in patients offers one of the most direct means of associating biochemical peculiarities with abnormal mental health. Even if drugs can be shown to block certain enzymes *in vitro*, for example, only by analysis of the pathways *in vivo* with and without drugs at clinical levels and with analysis for other major effects can general conclusions be drawn. And while advances have been possible with radioisotopic methods for the study of metabolic abnormalities, the power of such methods is greatly increased when the isotopic components are clearly separated and the unlabeled as well as the labeled compounds are quantitatively measured. Moreover since little is known about the biochemistry of thought processes, a general survey of metabolic products formed during mental stress offers a possible means for obtaining new information about such phenomena.

Proposed Course of Project: The urine of a large number of patients will be examined for peculiar metabolic products during relatively normal and abnormal periods. Brains of deceased patients will be compared to controls for unique chromatographic peaks which will be analyzed by the gas chromatograph/mass spectrometer. Finally the methods described above will be used with isotopic techniques in a general search for biochemical abnormalities which may be associated with depression, mania or schizophrenia.

Honors and Awards: None

Publications: None

Serial No. M-CS-OC(C)-19
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Metabolism, distribution and biochemical effects of psychoactive drugs

Previous Serial Number: None

Principal Investigators: Irwin J. Kopin and Julius Axelrod

Other Investigators: Louis Lemberger, L. Keng-Yong Ng (Guest Worker) and Robert W. Colburn

Cooperating Units: Sections on Pharmacology, Experimental Therapeutics and Medicine, LCS

Man Years: Total 1.5
Professional 1.1
Other 0.4

Project Description:

Methods Employed: (1) Drugs are administered; and using radioactivity or chemical methods, the levels in blood and in excretion in urine and feces are determined. (2) The alterations in amine metabolism are assessed by examining the tissues of animals or the blood, cerebrospiral fluid and urine of man. (3) The modification of effects of one drug by another is examined in animals.

Major Findings: Chlorpromazine and haloperidol reverse the effects of amphetamine on behavior of rats. Chlorpromazine but not haloperidol inhibits amphetamine metabolism. Tetrahydrocannabinol persists for several days in the blood of persons receiving the drug. Blood levels of the drug and its metabolites, which are rapidly formed, correlate well with the euphoric effects. Chronic marihuana smokers metabolize tetrahydrocannabinol more rapidly than others.

Significance to Biomedical Research and the Program of the Institute: The problem of drug usage is currently a major concern. The studies will help to elucidate the mechanisms of action of drugs which are abused, to indicate their possibly toxic effects and to suggest means for treatment of patients suffering from toxic effects of the drugs.

Proposed Course of Project: Identification of metabolites, estimation of drug effects on amine metabolism and enzymes concerned with amine synthesis and with degradation and examination of drug interactions will continue.

Honors and Awards: Dr. Lemberger presented the findings of the research team to the Symposium on Marijuana and its Surrogates (Federation of American Societies for Experimental Biology, Chicago/April 1971) and to the Conference on Marijuana (New York Academy of Sciences, New York/May 1971).

Drs. Kopin and Lemberger, in collaboration with investigators at the St. Elizabeth's Hospital, were invited to participate in a recorded interview on marihuana reserach for the Voice of America radio series; and Dr. Lemberger performed a similar service for the WGMS *Here's to Your Health* radio program.

Publications:

Lemberger, L., Witt, E.D., Davis, J.M. and Kopin, I.J.: The effects of haloperidol and chlorpromazine on amphetamine metabolism and amphetamine stereotype behavior in the rat. *J. Pharmacol. Exp. Ther.* 174:428-433, 1970.

Lemberger, L., Silberstein, S.D., Axelrod, J. and Kopin, I.J.: Marihuana: Studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. *Science* 170:1320-1322, 1970.

Lemberger, L., Axelrod, J. and Kopin, I.J.: The disposition and metabolism of tryptamine and the *in vivo* formation of 6-hydroxytryptamine in the rabbit. *J. Pharmacol. Exp. Ther.* 177:169-176, 1971.

Serial No. M-CS-M(C)-08
1. Laboratory of Clinical Science
2. Section on Medicine
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Formation, disposition and metabolism of biogenic amines and growth characteristics of aminergic neurons

Previous Serial Number: Same

Principal Investigator: Irwin J. Kopin

Other Investigators: Philippe V. Cardon, Robert W. Colburn, Hinrich Cramer (Guest Worker), Ingeborg Hanbauer, David P. Henry, David G. Johnson, Richard Kvetňanský (Guest Worker), Gertrude D. Maengwyn-Davies (Guest Worker), L. Keng-Yong Ng (Guest Worker), Sam Silbergeld, Stephen D. Silberstein, Nguyen B. Thoa, Theodore A. Walter (Guest Worker), August M. Watanabe and Virginia K. Weise

Cooperating Units: Section on Experimental Therapeutics, LCS and Units on Psychosomatics and Analytical Biochemistry (Office of the Chief), LCS

Man Years:		
	Total	11.0
	Professional	6.9
	Other	4.1

Project Description:

Objectives: (1) To determine the mechanisms which control development and plasticity of the nervous system. (2) To study the molecular basis for control of synthesis, storage, release, action and inactivation of aminergic transmitters. (3) To quantify metabolic rates for neurotransmitters and correlate them with function, drug effects and environmental influences.

Methods Employed: Radioactive amines or their precursors are injected into animals, perfused through tissues or exposed to tissue slices *in vitro*; and the metabolism and disposition of the compounds are examined. Enzymes concerned with synthesis or metabolism are assayed in various tissues; and the effects of drugs, procedures, age, etc. are determined. Tissues are grown *in vitro* in organ culture, and biochemical and histological features are correlated.

Major Findings: A variety of different stresses (immobilization, cold, electrical shock, attack by other animals) induces neuronally dependent elevations of tyrosine hydroxylase and dopamine-β-hydroxylase in the adrenal gland. Hormones of the adrenal cortex play a role in control of the levels of these catecholamine-synthesizing enzymes. The enzyme levels correlate well with the rate of catecholamine production. Release of catecholamines from sympathetic

nerve endings is accompanied by release of donamine-β-hydroxylase. This enzyme is synthesized in the cell body and transported to the nerve ending where it may control the rate of dopamine conversion to the actual transmitter. Ganglia grown in organ culture sprout new axons which can reinnervate sympathetically innervated tissues such as the iris. The sprouting and reinnervation appear to be triggered by nerve growth factor. A method for immunoassay of nerve growth factor has been developed and is being applied to study of developing nerves. Newly synthesized transmitter is selectively released, and the degree of mixing with the reserve stores of transmitter is dependent on the frequency of nerve stimulation. At slow rates of stimulation, mixing is more complete and the ratio of new to old norepinephrine more closely approximates that in the tissue.

In the guinea pig vas deferens, nerve stimulation enhances the rate of norepinephrine synthesis without altering the levels of tyrosine hydroxylase. Chlorpromazine interferes with this enhanced rate of synthesis by blocking dopmaine entry into the dopamine-β-hydroxylase-containing vesicles. Dopamine-β-hydroxylase is released during nerve stimulation, which is enhanced by phenoxybenzamine. This drug may have a previously unknown action on the mechanism of transmitter release.

Significance to Biomedical Research and the Program of the Institute: Catecholamines and other amines play an important role in normal physiology. Alterations in synthesis, activation, inactivation or metabolism of these substances may be responsible for abnormal clinical states or may explain the mode of action of drugs or development of tolerance or addiction to drugs. Assessment of these various processes is important in determining the factors influencing physiology, pharmacology and pathology in brain and other organs. Understanding the control mechanisms of development and plasticity provides further means of altering abnormal states.

Proposed Course of Project: Continued development of methods to study control and to quantify synthesis rates, storage, release and metabolic routes of the catecholamines in isolated tissues, intact animals and man and the study of these mechanisms of neurohumor inactivation in various clinical states of autonomic and mental disorders will be pursued. Studies of serotonin metabolism and release in nervous systems of mammals will continue. Assessment of the control of enzymes concerned with transmitter synthesis and their roles in control of neuronal function will be further studied. The development of synapses and axonal growth in the central and peripheral nervous systems will be studied *in vitro* to obtain a system which is easily controlled and is accessible for biochemical and neurophysiological study.

Honors and Awards: Dr. Kopin presented invited seminars on topics in catecholamine metabolism and synthesis to the Department of Pharmacology, University of Minnesota (Minneapolis), to the Divisions of Neurology/School of Medicine, Case Western Reserve University (Cleveland) and to the Department of Pharmacology, University of Colorado (Denver).

He served as Chairman of the session on Psychoactive Agents: Their Effects on Brain Amines and presented an address to the Symposium on Neurochemistry and Psychopharmacology of Affective Disorders and Schizophrenia (Houston: November 1970); he presented a series of daily lectures on Pharmacology of the Sympathetic Nervous System to the Department of Pharmacology/College of Medicine, University of Arizona (Tuscon: February 1971); and he presented a dissertation on The Use of Isotopes in Pharmacological Studies of Catecholamines to the Symposium on Use of Isotopes in the Diagnosis of Metabolic Disorders (Lake Geneva: March 1971).

Publications:

Krauss, K.R., Kopin, I.J. and Weise, V.K.: The effect of bretylium on amine retention in rat heart. *J. Pharmacol. Exp. Ther.* 172:282-288, 1970.

Krauss, K.R., Carpenter, D.O. and Kopin, I.J.: Acetylcholine-induced release of norepinephrine in the presence of tetrodotoxin. *J. Pharmacol. Exp. Ther.* 173:416-421, 1970.

Breese, G.R., Kopin, I.J. and Weise, V.K.: Effects of amphetamine derivatives on brain dopamine and noradrenaline. *Brit. J. Pharmacol.* 38:537-545, 1970.

Gewirtz, G.P. and Kopin, I.J.: Release of dopamine-β-hydroxylase with norepinephrine by splenic nerve stimulation. *Nature* 227:406-407, 1970.

Kvetňanský, R., Weise, V.K. and Kopin, I.J.: Elevation of adrenal tyrosine hydroxylase and phenylethanolamine-N-methyltransferase by repeated immobilization of rats. *Endocrinology* 87:744-749, 1970.

Louis, W.J., Krauss, K.R., Kopin, I.J. and Sjoerdsma, A.: Catecholamine metabolism in hypertensive rats. *Circulation Res.* 27:589-594, 1970.

Gewirtz, G.P. and Kopin, I.J.: Effect of intermittent nerve stimulation on norepinephrine synthesis and mobilization in the perfused cat spleen. *J. Pharmacol. Exp. Ther.* 175:514-520, 1970.

Kvetňanský, R., Gewirtz, G.P., Weise, V.K. and Kopin, I.J.: Effect of hypophysectomy on immobilization-induced elevation of tyrosine hydroxylase and phenylethanolamine-N-methyltransferase in the rat adrenal. *Endocrinology* 87: 1323-1329, 1970.

Kvetňanský, R., Gewirtz, G.P., Weise, V.K. and Kopin, I.J.: Enhanced synthesis of adrenal dopamine-β-hydroxylase induced by repeated immobilization in rats. *Molec. Pharmacol.* 7:81-86, 1971.

Paul, M.I., Kvetňanský, R., Cramer, H., Silbergeld, S. and Kopin, I.J.: Immobilization stress induced changes in adrenocortical and medullary cyclic-AMP content in the rat. *Endocrinology* 88:338-344, 1971.

Silbergeld, S., Kvetňanský, R., Sigalos, G.L., Weise, V.K. and Kopin, I.J.: Levels of adrenal catecholamine-synthesizing enzymes after postmortem treatment in rats and after necropsy in human beings. *J. Lab. Clin. Med.* 77:290-297, 1971.

Gewirtz, G.P., Kvetňanský, R., Weise, V.K. and Kopin, I.J.: Effect of hypophysectomy on adrenal dopamine-β-hydroxylase activity in the rat. *Molec. Pharmacol.* 7:163-168, 1971.

Johnson, D.G., Thoa, N.B. and Kopin, I.J.: Inhibition of norepinephrine biosynthesis by chlorpromazine in the guinea pig vas deferens. *J. Pharmacol. Exp. Ther.* 177:146-154, 1971.

Gewirtz, G.P., Kvetňanský, R., Weise, V.K. and Kopin, I.J.: Effects of ACTH and dibutyryl cyclic-AMP on catecholamine-synthesizing enzymes in the adrenals of hypophysectomized rats. *Nature* 230:462-463, 1971.

Serial No. M-CS-M(C)-11
1. Laboratory of Clinical Science
2. Section on Medicine
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: False neurochemical transmitters and the mechanism of transmitter release

Previous Serial Number: Same

Principal Investigator: Irwin J. Kopin

Other Investigators: Philippe V. Cardon, David G. Johnson, L. Keng-Yong Ng (Guest Worker), Nguyen B. Thoa, August M. Watanabe and Virginia K. Weise

Cooperating Units: Units on Psychosomatics and Analytical Biochemistry (Office of the Chief), LCS and Section on Experimental Therapeutics, LCS

Man Years:		
	Total	1.5
	Professional	1.0
	Other	0.5

Project Description:

Objectives: To determine the consequences of neurochemical transmitter replacement by relatively inactive substances, "false transmitters," in the mechanism of action of drugs, to study the possible role of these substitute transmitters in disease states and to investigate the mechanism of transduction of the nerve impulse into transmitter release.

Methods Employed: (1) Radioactively labeled substances which are known or thought to accumulate in sympathetic nerves are synthesized and purified. (2) The central effects of ℓ-dopa have been studied in animals in which the adrenergic and dopaminergic neurons have been destroyed with 6-hydroxydopamine. This permits study of uptake and metabolism of dopa and dopamine in serotonergic neurons. (3) The central effects of dopa on cardiovascular reflexes mediated by the central nervous system are examined in animals and man.

Major Findings: Amines related to norepinephrine can replace it at its binding sites and thereby influence norepinephrine synthesis, storage and release. The effects depend on the time after administration. Dopamine, formed from dopa, in serotonergic neurons can displace serotonin and diminish synthesis and release of this indoleamine. Dopamine may be a false serotonergic transmitter.

Significance to Biomedical Research and the Program of the Institute: An understanding of the mechanisms for binding and release of catecholamines is basic to a meaningful hypothesis of the events related to the activation of transmitters and synaptic transmission. The fact that a number of inactive substances chemically related to norepinephrine may replace it provides a means for modulating the effects of nerve stimulation. Drugs such as the monoamine oxidase inhibitor α-methyldopa may result in accumulation of false transmitters and exert their effects indirectly. It is possible that after drug administration or in disease states, endogenously formed false transmitters may reduce effectiveness of neurotransmission through certain nervous pathways. Other steps in the transduction of the nerve impulse to transmitter release may also be affected (as with bretylium). Amphetamine tolerance may be due to accumulation of p-hydroxynorephedrine, a metabolite of amphetamine, which may be a false adrenergic transmitter in the central nervous system.

Proposed Course of Project: Further investigations of the stoichiometry of norepinephrine replacement by false transmitters and of intermediate processes between arrival of the nerve impulse and transmitter release and a search for cholinergic or serotonergic false transmitters are planned. The possible existence of other molecular substitutes (hormones, for example) will also be investigated. Studies on the possible role of false transmitters in drug action in man are planned.

Honors and Awards: Dr. Kopin presented an invited seminar on Catecholamines as neurotransmitters in brain and a lecture on Biogenic amines and drug action to the Department of Pharmacology/School of Medicine, UCLA Center for the Health Sciences (Los Angeles: January 1971). As 1970 President, he presented a paper on Aminergic neurons and substitute transmitters in brain to the annual meeting of the Association for Research in Nervous and Mental Disease (December 1970). He was also appointed to the Commission on Neurotransmission of the International Union of Physiological Sciences.

Publications:

Breese, G.R., Chase, T.N. and Kopin, I.J.: Effect of monoamine oxidase inhibitors on the disposition of intracisternally administered metaraminol-^{3}H. *Biochem. Pharmacol.* 19:525-532, 1970.

Kopin, I.J.: Accumulation of drugs at sympathetic nerve endings. In Brodie, B.B. and Gillette, J.R. (Eds.): *Handbook of Experimental Pharmacology, Vol. XXVIII/1* (Concepts in Biochemical Pharmacology). New York: Springer/Verlag, 1971 (pp. 317-327).

Serial No. M-CS-Ps(C)-18
1. Laboratory of Clinical Science
2. Section on Psychiatry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biochemical and behavioral factors in affective disorders

Previous Serial Number: Same

Principal Investigator: William E. Bunney, Jr.

Co-Principal Investigators: Dennis L. Murphy, Frederick K. Goodwin

Other Investigators: David L. Dunner, Elliot S. Gershon, George M. Henry, Max A. Baker, Thomas C. Goldman, Kenneth M. House, Joel Kotin, Robert M. Post

Biochemists: Edna K. Gordon

Other Collaborating Scientists: Michael Paul, Monte S. Buchsbaum, Frederick Snyder, Richard Wyatt, Allan Beigel, H.K.H. Brodie, George Borge

Psychiatric Social Workers: Yolande Davenport, Carol F. Hoover

Psychiatric Consultants: M.B. Richmond, P. Chodoff, M.L. Adland, H.A. Myersberg

Art Therapist: Harriet S. Wadeson

Cooperating Units: Nursing, Occupational Therapy Personnel on Wards 3-East and 4-West

Man Years:

Total	18.6
Professional	11.6
Other	7.0

Project Description:

Objectives: The objective of these projects has been to develop a research program for the investigation of the behavioral, biochemical and physiological aspects of depressive and manic-depressive patients.

Behavioral Objectives: Behavioral objectives include an attempt to delineate some of the central problems in depression. This involves an

intensive analysis of the environmental and psychological events occurring prior to and during the development of depressive and manic illness.

Biochemical and Pharmacological Objectives: Biochemical objectives involve testing the hypothesis that norepinephrine, dopamine and/or serotonin are decreased in depressed patients and are increased in manic patients. An attempt is being made to develop methods for studying the metabolism of the putative neurotransmitters in human brain. In part this involves the utilization of pharmacological agents which effect enzymes involved in the synthesis and breakdown of these neurotransmitters.

Methods Employed:

1. Both manic-depressive and depressive patients are selected for study. The depressed patients demonstrate feelings of hopelessness, thoughts of worthlessness, preoccupation with death and dying, and difficulty sleeping, while the manic patients often show flight of ideas, grandiosity, inappropriate behavior and, at times, euphoria.

2. Behavioral and biochemical data is collected on a longitudinal basis throughout the course of each patient's hospitalization.

3. Behavioral data is collected by a nursing research team, the social worker, and ward physicians.

a. The nursing research team is trained in systematic methods of observation and recording. At the end of each morning and evening shift, two members of the nursing team independently rate each patient on a 15-point scale. The scale measures the amount of depression, anxiety, psychotic behavior, physical activity, somatic complaints and anger which are manifested during the 8-hour shift. A separate scale has been developed for the measurement of manic symptomatology. The nurses also describe the patients' verbal and non-verbal behavior every eight hours.

b. The staff physicians see each patient in individual psychotherapy two to four times a week. The physicians dictate information following a schedule after each therapy session.

c. The social worker interviews the closest relatives of each patient and sees them individually on a weekly basis.

d. Observations are made by the nurses concerning the patients' sleep throughout every night. These observations are recorded at half-hour intervals.

Biochemical Data: 24-hour urine pools are collected throughout hospitalization for the determination of urinary catecholamines and indoleamines and their metabolites. Cerebrospinal fluid was obtained from some patients and was analyzed for the metabolites of catechol- and indoleamines. Some patients were given doses of probenecid as a research procedure. Probenecid

inhibits the active transport of acid metabolites of brain amines, 5-hydroxy-indoleacetic acid (5HIAA) and homovanillic acid (HVA), the major breakdown products of serotonin and dopamine, respectively. The CSF levels of these acid metabolites are closely related to brain levels and their rate of accumulation during probenecid administration can be used as an indirect index of amine turnover.

Physiological Data: Some of the patients are monitored in terms of their EEG and rapid eye movement potentials throughout each night in a collaborative study with Dr. Frederick Snyder.

Pharmacological Studies: Active medication and placebo were administered double-blind in a non-random design to many of the patients, with placebo substitution before and after each active compound. The utilization of placebo substitution increased the level of confidence in the efficacy of a compound in an individual patient. This is important in the evaluation of drug effects because of the frequency of spontaneous remissions and exacerbations in manic-depressive illness.

Major Findings: The major findings in the Section during the past year can be conveniently discussed under five general categories: 1) studies of the steady state of mania and the switch into and out of mania; 2) pharmacological studies in the treatment of depression; 3) studies of brain function and psychoactive drugs; 4) studies of memory and learning in relationship to psychoactive drugs and change in clinical state; and, 5) laboratory studies.

1. STUDIES OF THE STEADY STATE OF MANIA AND THE SWITCH INTO AND OUT OF MANIA: A program has been projected over the next few years to continue our investigations of the manic phase in the manic-depressive illness and to study the point of change from depression into mania and from mania into depression. A manic-state rating scale has been developed and its reliability and validity determined during the last year. The scale provides a more useful method to quantitate the severity of manic behavior and determine sub-components of manic behavior which may be preferentially altered by different psychoactive drugs. In addition, the scale has been shown to discriminate two sub-groups of manic patients, one with prominent elation and grandiosity and another with low ratings on these symptoms but higher ratings of paranoia and destructive behavior. The existence of depressive affect during manic behavior has also been documented in the majority of manic patients.

A regular pattern of change in thought and mood was documented during spontaneous episodes of switch from depression into mania and episodes of switches from mania into depression. We operationally defined the events occurring at the time of change from one predominant affective state to another as the "switch process". The depressive period prior to the switch into mania was characterized by moderate depression, seclusiveness, non-verbalization and dozing. Each of the episodes of mania was preceded by a normal or transitional period which was manifested by the sudden appearance of spontaneous speech, motor activity and normalization of mood. Impending

discharge from the hospital occurred just prior to the episodes of mania and they may thus represent a specific environmental stress associated with the onset of mania. During the switches from mania into depression the patient showed the following sequence of behavior: mania, hypomania, a short unstable transitional period, followed by retarded depression.

Total hours of sleep were markedly reduced on the day prior to the switch into mania and remained low during the manic period.

During the switch into mania, it was further shown that urinary norepinephrine was significantly elevated on the day prior to and during the manic episode. Similar trends were noted for epinephrine and dopamine. Urinary adenosine 3', 5'-monophosphate (cyclic-AMP) was shown to be increased on the day of the switch from depression into mania. There was a statistically significant increase on the day of the change in the seven patients studied when this mean value was compared with the days prior to the switch. It has been shown that changes in cyclic-AMP may be related to alterations in amine metabolism.

Brief administration of tricyclic medication was associated in a few patients with rapid switches from depression into a short normal period and then into manic behavior. These switches into mania were behaviorally identical with those nondrug-associated switches which were observed. Tricyclic compounds probably increase functional brain norepinephrine and dopamine by inhibiting the neuronal uptake of these neurotransmitters. In bipolar patients with past histories of mania, brief hypomanic episodes were regularly associated with the administration of large doses of dihydroxyphenylalanine (L-DOPA), the specific metabolic precursor of dopamine and norepinephrine. In a small group of bipolar patients treated with large doses of L-tryptophan, hypomania did not occur.

Alpha-methyl-para-tyrosine (aMPT), a specific inhibitor of the synthesis of norepinephrine and dopamine, was associated with a rapid transitory decrease in mania in a few patients. In only two patients, however, was there an increase in symptoms when placebo was substituted. It failed to be effective in other patients.

These findings support an important role for the catecholamine neurotransmitters, dopamine and norepinephrine, in the switch process of the manic-depressive illness.

2. PHARMACOLOGICAL STUDIES IN THE TREATMENT OF DEPRESSION: Large doses of L-DOPA were administered with and without a peripheral decarboxylase inhibitor, alpha-methyl-DOPA-hydrazine (MK485) to 23 depressed patients. Only 25% of the total group showed a consistent improvement in depression on L-DOPA. Prior to treatment all of the responders were retarded. An intensification of existing psychotic symptoms with L-DOPA was noted in the psychotically depressed patients who did not show a therapeutic response. Drs. Dunner and Goodwin have studied plasma DOPA levels in depressed patients after the administration of L-DOPA with and without MK485. A potentiation of the half-

life of plasma DOPA was found with MK485. A reduction to about one-tenth of the L-DOPA dose was needed to achieve the same half-life when MK485 was given.

Large doses of L-tryptophan were administered to ten depressed patients. Only three patients clearly responded to the medication, thus suggesting that in this patient population it was less effective than previously reported in the literature. In a further attempt to test the catecholamine hypothesis, aMPT was administered to six depressed patients. One patient with a prior history of mania and three without prior histories of mania became worse on aMPT and two patients showed no change.

We have continued to investigate the antidepressant response to lithium and have now studied 52 patients. Data clearly indicated differential responses in the unipolar vs. bipolar patients, in that in the bipolar patient group there is a higher frequency of antidepressant responses as compared to the unipolar group.

3. STUDIES OF BRAIN FUNCTION AND PSYCHOACTIVE DRUGS: Studies of cerebrospinal fluid levels of 5HIAA, the major breakdown product of serotonin, have revealed a consistent decrease in our group of depressed patients as compared with neurological patients.

During the past year a good deal of effort has been devoted, primarily on 4-West by Drs. Goodwin and Dunner, to the further validation of the probenecid method for the estimation of amine turnover in the brains of patients. Probenecid blocks the active transport of amine metabolites out of the central nervous system and, thus, the accumulation of acid metabolites following probenecid block can be used as an estimate of the rate at which the parent amines are being synthesized (turnover rate). It was shown that the administration of L-DOPA with MK485 is associated with an increase in the turnover of dopamine and a decrease in the turnover of serotonin. Large doses of tryptophan, the metabolic precursor of serotonin, caused a marked elevation in the rate of accumulation of 5HIAA on probenecid. This information is important since other research groups have recently suggested that there may be a deficiency of tryptophan hydroxylation in depressed patients which could be used as an explanation for the lack of clinical efficacy of tryptophan in this group of individuals. However, our data from the probenecid experiments indicate that a considerable amount of the administered tryptophan is being converted to serotonin and broken down to the major metabolite, 5HIAA. Thus, the lack of clinical efficacy of tryptophan in our patients cannot easily be explained on the basis of a tryptophan hydroxylase deficiency.

As would be predicted, patients who were on probenecid and who received aMPT showed little or no elevation of HVA, the breakdown product of dopamine.

Studies of REM time provided an additional index of brain metabolism. In our attempts to study the biochemistry of REM sleep, we have administered i.v. L-DOPA before, during and after REM sleep. I.V. L-DOPA clearly decreased the length of REM periods and increased the latency prior to the onset of the first REM. In a number of instances, REM sleep was terminated within 15 seconds

after 25mg of i.v. L-DOPA.

4. STUDIES OF MEMORY AND LEARNING IN RELATIONSHIP TO PSYCHOACTIVE DRUGS AND CHANGE IN CLINICAL STATE: Quantitative measures of verbal learning and word association have been obtained in cycling manic-depressive patients by Drs. George Henry and Dennis Murphy, in collaboration with Dr. Herbert Weingartner of the University of Maryland. Learning was markedly impaired during mania compared to both non-manic periods in the same patient and to the performance of normal controls. Regression analysis indicated that increased mania was associated with reduced learning performance and with a decrease in the percentage of high frequency associative responses, and an increase in the percentage of idiosyncratic associations. During mania, patients gave 33% idiosyncratic association responses, a three-fold increase over non-manic and control subject responses and nearly double the percentage of idiosyncratic responses reported in other studies with schizophrenics, drug-induced psychosis and psychotic depressives. It is proposed that a reversible process specific to the manic state alters patterns of verbal association toward idiosyncratic meaning, thereby predictably interfering with the long-term memory processes, particularly retrieval. In studies with psychoactive drugs, L-DOPA has been found to enhance verbal learning in depressed patients receiving large oral doses of this catecholamine precursor. Studies with aMPT, L-tryptophan and other drugs are in progress.

5. LABORATORY STUDIES: Dr. Dunner in this Section has completed a collaborative study with Dr. Axelrod's Section on red blood cell catechol-O-methyl-transferase (COMT) activity in depressed patients separated into unipolar and bipolar groups. Women with unipolar illness had the lowest COMT activity while women with bipolar illness had intermediate activity between the unipolar women and the control group.

Dr. Dennis Murphy has been involved in studies of biogenic amine transport and metabolism in man. Blood platelets contain amines and amine-related enzymes and thus provide a model system for studies of the effect of psychoactive drugs on their cellular function in man. L-DOPA and L-tryptophan administration have been found to affect serotonin levels in platelets from patients receiving the drugs, with L-tryptophan increasing serotonin content and L-DOPA decreasing it. Monoamine oxidase (MAO) levels in platelets vary widely in different individuals. Some depressed patients have MAO levels nearly as low as those found in patients receiving MAO-inhibiting drugs. The possibility that false transmitters may accumulate in platelets (and possibly neurons) in these patients with low MAO activity is under investigation.

Drs. Gershon and Goodwin have continued their studies on the effects of various pharmacological agents on the turnover of brain amines in rats. They have found that L-DOPA accelerates the turnover of both dopamine and norepinephrine (NE) in the brain whereas tyrosine does not. This year a good deal of effort has gone into improvement in the methodology for the study of brain amine turnover. For example, it has been found that when H^3-dopamine is used to label the endogenous NE pool rather than C^{14}-NE, one gets different results in terms of drug effects on NE turnover.

Proposed Course of Project: During the next year, continued emphasis will be given to the investigation of the switch process and to the manic phase of the manic-depressive illness.

A study of twins discordant for manic-depressive illness has been designed and will be undertaken in collaboration with Drs. William Pollin and Lyman Wynne.

Further studies have been planned using additional pharmacological agents to study the biochemistry of REM sleep.

Finally, new studies will be undertaken in the next year in the area of drug addiction, in collaboration with Dr. Irwin Kopin. These investigations will focus on a number of compounds, including cocaine and THC. There is a particular interest in the Section concerning the biochemistry of the experience of "high". Mania may offer a paradigm for the study of other highs, including drug-induced euphoria, which has been associated with compounds such as cocaine, amphetamines and heroin. One might hypothesize that the various types of "high" may have common underlying biochemical changes.

HONORS AND AWARDS

Drs. William E. Bunney, Jr., Frederick K. Goodwin and Dennis L. Murphy were recipients of a First Place Research Award from the Division of Psychopharmacology of the American Psychological Association in 1970. Drs. Bunney, Goodwin and Murphy have also been chosen as First Place co-winners of the 1971 Hofheimer Research Award given by the American Psychiatric Association.

Dr. Bunney presented a paper on "Biochemical Studies of Manic-Depressive Illness" at the Karolinska Institute, Stockholm, Sweden, a paper entitled, "Drugs Associated with the Switch Process from Depression to Mania" at the 7th Congress of the C.I.N.P., in Prague, Czechoslovakia, a paper entitled, "L-DOPA in Depression" to the American College of Neuropsychopharmacology in San Juan, Puerto Rico, and a paper entitled, "Biochemistry of the Depressive State" in a Symposium on Separation and Depression, Clinical and Research Aspects, at the American Association for the Advancement of Science in Chicago. Dr. Bunney was invited to present a paper to a Colloquium at the University of Rochester School of Medicine, and he was an invited speaker at a Symposium on Depression sponsored by Excerpta Medica in New York City. He participated as a member of the Commission of the Association for Research in Nervous and Mental Disease in December, 1970. Dr. Bunney also organized and moderated a Combined Clinical Staff Conference on Manic-Depressive Illness in the Clinical Center, NIH, and presented a paper entitled, "The Switch Process into Mania: Theoretical Implications for Manic-Depressive Illness".

Dr. Goodwin presented a paper entitled, "L-DOPA in Combination with a Peripheral Decarboxylase Inhibitor in Depression" to the 7th Congress of the C.I.N.P. in Prague, Czechoslovakia, and was co-author of several other papers presented at the meeting by other members of the Section. He presented a paper, "The Use of Probenecid to Study Brain Amine Turnover in Man" at the Winter Conference on Brain Research in Aspen, Colorado, in January, 1971, a paper entitled, "Response to Lithium in Bipolar vs. Unipolar Depression" at the Scientific Proceedings of the American Psychiatric Association, and a paper, "L-DOPA in Depression" was presented in Montreal, Quebec to the Psychiatric Research Society. "L-DOPA: Alterations in Mood" was presented at a Symposium on L-DOPA, held by the American Society of Clinical Pharmacology and Therapeutics, University of Pennsylvania, Philadelphia. Dr. Goodwin also presented papers at the Symposium on Mood, Behavior and Drugs of the Annual Meeting of the American Association for the Advancement of Science, Chicago, to the Department of Psychiatry, University of California at Davis, and to the Department of Psychiatry, University of California at San Diego in La Jolla. In addition, he co-authored papers which were presented at the Fall Meeting of the American Society of Pharmacology and Experimental Therapeutics.

Dr. Murphy presented a paper, "Psychiatric Aspects of L-DOPA Treatment" to the Association for Research in Nervous and Mental Disease Annual Meeting in New York. He was guest lecturer at the George Washington University School of Medicine and spoke on "Manic-Depressive Illness: Clinical Features

and Treatment". He gave a guest lecture at St. Elizabeth's Hospital, Washington, D.C. on "L-DOPA, Catecholamines and Behavior" and will present a paper at the annual meeting of the American Psychiatric Association in Washington, D.C. on "Amine Precursors, Monoamine Oxidase Activity and False Neurotransmitters in Depressed Patients". In addition, Dr. Murphy participated in the NIH Combined Clinical Staff Conference on Manic-Depressive Illness and presented a paper entitled, "Behavioral Activating Effects of L-DOPA".

Dr. Gershon will present a paper at the American Psychiatric Association Annual Meeting in Washington, D.C. entitled, "Assortative Mating in the Affective Disorders". He presented a paper before the meeting of the Society for Experimental Therapeutics in Palo Alto, California, entitled "Effect of L-Tyrosine and L-DOPA on Norepinephrine Turnover in Rat Brain in vivo" in August, 1970.

Dr. Henry lectured to the NIMH Fellows in Suicidology, St. Elizabeth's Hospital, Washington, D.C. on "Biochemical Studies of Depression and Suicide", and to the staff of Northern Virginia Mental Health Institute, Fairfax, Virginia, on "Assessing and Treating the Suicidal Patient". He participated in the NIH Combined Clinical Staff Conference on Manic-Depressive Illness and talked on "Clinical Studies Differentiating Two Subgroups of Affective Illness". In addition, Dr. Henry was interviewed about "Current Studies and Treatment of the Mood Disorders" on Station WGMS' Program, "Here's to Your Health", in Washington, D.C.

Baer, L.; Durell, J., Bunney, W.E., Jr., Levy, B.S., Murphy, D.L., Greenspan, K., and Cardon, P.V.: Sodium balance and distribution following lithium therapy in affective disorders. Arch. Gen. Psychiat. 22:40-44, 1970.

Bunney, W.E., Jr.; Carpenter, W.T., Engelman, K., and Davis, J.M.: Brain serotonin and depressive illness. In Proceedings of the NIMH Workshop on Recent Advances in the Psychobiology of the Depressive Illnesses Washington, D.C., Government Printing Office, 1971.

Mueller, P.S.; Davis, J.M., Bunney, W.E., Jr., Weil-Malherbe, H., and Cardon, P.V.: Plasma free fatty acid concentrations in depressive illness. Arch. Gen. Psychiat. 22:216-221, 1970.

Leff, M.J.; Roatch, J.F., and Bunney, W.E., Jr.: Environmental factors preceding the onset of severe depressions. Psychiatry 33:293-311, 1970.

Bunney, W.E., Jr.; Borge, G.F., Murphy, D.L., and Goodwin, F.K.: The switch process from depression to mania: relationship to drugs which alter brain amines. Lancet I:1022-1027, 1970.

Bunney, W.E., Jr.; Murphy, D.L., and Goodwin, F.K.: Further studies with L-DOPA in depressed patients. Lancet I:352, 1970.

Paul, M.I.; Cramer, H., and Bunney, W.E., Jr.: Urinary cyclic-AMP in the switch process from depression to mania. Science 171:300-303, 1971.

Brodie, H.K.H.; Murphy, D.L., Goodwin, F.K., and Bunney, W.E., Jr.: Alpha-methyl-para-tyrosine as a treatment for mania. In Proceedings of the 7th Congress of the C.I.N.P.(Prague, 1970), Excerpta Medica Foundation, International Congress Series. In Press.

Bunney, W.E., Jr.: Biochemical research in affective illness. In: Fieve, R. (Ed.) Depression 1970. New York, Excerpta Medica Foundation. In Press.

Brodie, H.K.H., Murphy, D.L., Goodwin, F.K., and Bunney, W.E., Jr.: Catecholamines and mania: the effect of alpha-methyl-para-tyrosine on manic behavior and catecholamine metabolism. Clin. Pharmacol. Ther. 12:218-224, 1971.

Bunney, W.E., Jr.; Brodie, H.K.H., Murphy, D.L., and Goodwin, F.K.: Studies of alpha-methyl-para-tyrosine, L-DOPA, and L-tryptophan in depression and mania. Amer. J. Psychiat. 127:48-57, 1971.

Bunney, W.E., Jr.; Murphy, D.L., and Goodwin, F.K.: Psychopharmacological studies of L-DOPA. Presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, 1970, In: Malitz, S. (Ed.) L-DOPA and Behavior. New York, Raven Press, In Press.

Bunney, W.E., Jr.; Gershon, E.S., Murphy, D.L., and Goodwin, F.K.: Psychobiological and pharmacological studies of manic-depressive illness. J. Psychiat. Res. In Press.

Murphy, D.L.; Goodwin, F.K., and Bunney, W.E., Jr.: Electrolyte changes in the affective disorders: Problems of specificity and significance. In Recent Advances in the Psychobiology of the Depressive Illness. Washington, D.C., Government Printing Office, 1971, pp. 62-73.

Murphy, D.L.; Colburn, R.W., Davis, J.M., and Bunney, W.E., Jr.: Imipramine and lithium effects on biogenic amine transport. Amer. J. Psychiat. 127: 339-345, 1970.

Murphy, D.L.; Brodie, H.K.H., Goodwin, F.K., and Bunney, W.E., Jr.: L-DOPA: regular induction of hypomania in bipolar manic-depressive patients. Nature 229:125-136, 1971.

Murphy, D.L.; Goodwin, F.K., Bunney, W.E., Jr.: Leukocytosis during lithium treatment. Amer. J. Psychiat. 127:118-120, 1971.

Murphy, D.L.; and Kopin, I.J.: The transport of biogenic amines. In: Hokin, L.E. (Ed.) Cell Transport and Metabolism. New York, Academic Press. In Press.

Murphy, D.L.; Bunney, W.E., Jr.: Total body potassium changes during lithium treatment. J. Nerv. Ment. Dis. In Press.

Murphy, D.L.: L-DOPA, behavioral activation and psychopathology. In Research Proceedings, Association for Research in Nervous and Mental Disease. In Press.

Goodwin, F.K.; Brodie, H.K.H., Murphy, D.L., and Bunney, W.E., Jr.: L-DOPA, catecholamines and behavior: a clinical and biochemical study in depressed patients. (A.E. Bennett Prize Paper). Biol. Psychiat. 2:341, 1970.

Paul, M.I.; Cramer, H., and Goodwin, F.K.: Urinary cyclic-AMP in depression and mania: effects of L-DOPA and lithium carbonate. Arch. Gen. Psychiat. In Press.

Tamarkin, N.R.; Goodwin, F.K., and Axelrod, J.: Rapid elevation of biogenic amine metabolites in human CSF following probenecid. Life Sci. 9:1397, 1970.

Goodwin, F.K.: Psychiatric effects of L-DOPA in man. Read at the Symposium on L-DOPA, Annual Meeting American Medical Association, Chicago, 1970, JAMA. In Press.

Goodwin, F.K.; Murphy, D.L., Brodie, H.K.H., and Bunney, W.E., Jr.: Levodopa: alterations in behavior. Clin. Pharmacol. Ther. 12:383-396, 1971.

Borge, G.; Buchsbaum, M., Goodwin, F.K., et al.: Neuropsychological correlates of affective disorder. Arch. Gen. Psychiat. In Press.

Gershon, E.S.; Dunner, D.L., and Goodwin, F.K.: Toward a biology of affective illness: genetic contributions. Arch. Gen. Psychiat. In Press.

Goodwin, F.K.: Behavioral effects of L-DOPA in man. In Seminars in Psychiatry. In Press.

Gershon, E.S.; Bunney, W.E., Jr., Goodwin, F.K., et al.: Catecholamines and affective illness: studies with L-DOPA and alpha-methyl-para-tyrosine. In: Ho, B.T. and McIsaac, W.M. (Eds.) Brain Chemistry and Mental Disease. In Press.

Buchsbaum, M.; Goodwin, F.K., Murphy, D.L., and Borge, G.: Average evoked response in affective disorders. Amer. J. Psychiat. In Press.

Goodwin, F.K.; and Bunney, W.E., Jr.: Behavioral effects of reserpine in man. Seminars in Psychiatry. In Press.

Goodwin, F.K.; and Bunney, W.E., Jr.: Psychobiology of affective illness. Presented at the Annual Meeting, American Association for the Advancement of Science, 1970. In: Senay, E. (Ed.) Separation and Depression. Plenum Press. In Press.

Beigel, A.; and Murphy, D.L.: Unipolar and bipolar affective illness. Arch. Gen. Psychiat. 24:215-220, 1971.

Beigel, A.; Murphy, D.L., and Bunney, W.E., Jr.: The manic-state rating scale: scale construction, reliability, and validity. Arch. Gen. Psychiat. In Press.

Dunner, D.L.; Brodie, H.K.H., and Goodwin, F.K.: Plasma DOPA response to levodopa administration in man: effects of a peripheral decarboxylase inhibitor. Clin. Pharmacol. Ther. 12:212-217, 1971.

Dunner, D.L.; Cohn, C.K., Gershon, E.S., and Goodwin, F.K.: Differential catechol-O-methyltransferase activity in unipolar and bipolar affective illness. Arch. Gen. Psychiat. In Press.

Carpenter, W.T.; and Bunney, W.E., Jr.: Adrenal cortisol activity in depressive illness. Amer. J. Psychiat. In Press.

Carpenter, W.T.; and Bunney, W.E., Jr.: Diurnal rhythm of cortisol in mania. Arch. Gen. Psychiat. In Press.

Serial No. M-CS-Ph-3
1. Laboratory Of Clinical Science
2. Section on Pharmacology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Cellular mechanisms in the metabolism of drugs and hormones.

Previous Serial Number: Same

Principal Investigators: Julius Axelrod, Ira B. Black, W. Stephen Brimijoin, Cal K. Cohn, Joseph T. Coyle, Perry B. Molinoff, Richard M. Weinshilboum

Other Investigators: Donald J. Reis (Guest Worker), Klaus Brandau (Guest Worker), Svante Ross (Guest Worker), James P. Henry

Cooperating Units: Cornell University Medical College; Pharma-Research Centre, Farbenfabriken Bayer, Germany; Astra Läkemedel, Sweden; Department of Physiology, University of Southern California.

Man Years:

Total	11
Professional	7
Others	4

Project Description:

Objectives: To study the enzymes involved in the formation and metabolism of hormones and drugs, and to examine how these enzymes are regulated. To develop methods for the detection of enzymes in the blood of humans and to examine these changes in different physiological, pharmacological and disease states.

Methods Employed: Biochemical, pharmacological and radioactive tracer techniques.

Major Findings: A considerable part of the work of the Section on Pharmacology has been concerned with a search for enzymes involved in biogenic amine biosynthesis and metabolism in an easily accessible tissue, the blood. This made it possible to study changes in these enzymes in man and other species under differerent physiological conditions and in disease.

Dopamine-β-oxidase, an enzyme highly localized in storage granules of sympathetic nerves, was found to be circulating in the plasma of man and other species. The enzyme is elevated in the plasma of man and rat during stress and decreased in rats after destruction of sympathetic nerve terminals with 6-hydroxydopamine. There is no change in plasma dopamine-β-oxidase after removal of the adrenal glands. This suggests that plasma dopamine-β-oxidase arises mainly from the sympathetic nerves.

Preliminary studies indicate that plasma dopamine-β-oxidase is decreased in familial dysautonomia.

An assay for the measurement of dopamine-β-oxidase has been developed for the brain. Highest concentration of the enzyme was found in the brain stem and hypothalamus and lowest in the corpus striatum. Lesions made in the lateral hypothalamus results in a fall of dopamine-β-oxidase in the ipsilateral areas of the telencephalon.

The development of the noradrenergic neurons has been examined in the fetal and neonatal rat brain. By using the specific neuronal reuptake mechanism for norepinephrine as a marker for the nerve terminals, it has been demonstrated that the noradrenergic nerve terminals first appear four days prior to birth and attain an adult concentration by four weeks after birth. The ability for nerve terminals to store norepinephrine in vesicles develops more slowly. Dopamine-β-hydroxylase, the last enzyme in the synthesis pathway for norepinephrine, is already present seven days prior to birth. During the last week of gestation, it is found primarily in the brain stem where the cell bodies for the noradrenergic neurons are located; but, as the nerve terminals grow out, the activity of dopamine-β-hydroxylase increases in other areas of the brain. In the adult, the enzyme has been demonstrated to be tightly bound to the storage vesicles, and 70% of the enzyme is located in the nerve terminals.

Destruction of nerve terminals with 6-hydroxydopamine results in a decrease of dopamine-β-oxidase in the sympathetic ganglia and prevents reserpine-induced increases in the activity of dopamine-β-oxidase and tyrosine hydroxylase. A number of drugs including reserpine and 6-hydroxydopamine were shown to increase the activity of tyrosine hydroxylase and dopamine-β-oxidase by a mechanism involving both protein synthesis and neuronal transmission. The induction of these enzymes was blocked by agents which raise the level of noradrenaline, suggesting that catecholamines are involved in the formation of these enzymes.

The following enzymes were found to be present in red blood cells of man and other species; catechol-O-methyltransferase, histamine-N-methyltransferase, methanol-forming enzyme and methionine-activating enzyme. Red blood cell catechol-O-methyltransferase were lower in women (but not men) who have both mania and depression. Patients treated with L-dopa have a decreased red blood cell catechol-O-methyltransferase. Histamine-N-methyltransferase is elevated in patients with manic depression or schizophrenia.

Using starch block electrophoresis, dopamine-β-oxidase was found to be separated in a bound-free form. Dopamine-β-oxidase from different species have different electrophoretic mobilities.

The circadian rhythm in tyrosine transaminase is regulated by both adrenergic and cholinergic nerves. Adrenergic nerves suppress the enzyme and cholinergic nerves stimulate the enzyme.

Octopamine has been shown to be released on nerve stimulation together with noradrenaline.

Significance to Biomedical Research and the Program of the Institute:

The measurement of enzymes in human blood has made it possible to study the activity of the sympathetic nervous system in man in stress and in a number of diseases (manic depression, familial dysautonomia) and after drug treatment.

The development of a sensitive assay for octopamine has shown that it may be a neurotransmitter.

Work on development of the adrenergic neurones in the fetal brain has given considerable insight into the sequence of outgrowth of these important nerves in the brain.

Proposed Course of Project: Search will be made for other enzymes in blood. Changes in blood dopamine-β-oxidase, catechol-O-methyltransferase, histamine N-methyltransferase, methanol-forming enzyme and methionine-activating enzyme will be examined in changing physiological conditions and in different diseases.

The cellular mechanism for the development of the adrenergic nerves in rat brain will be continued. Effects of drugs and hormones, etc., on this development will be examined.

The mechanisms for the induction and regulation of tyrosine hydroxylase, dopamine-β-oxidase, phenylethanolamine and methyltransferase in the nerve and adrenal will be explored. Effects of different psychosocial stimulations on blood pressure and catecholamine biosynthetic enzymes will be studied.

Honors and Awards: Dr. Axelrod has been asked to give the Parkinson lecture, Columbia University; Bennett lecture, American Academy of Neurology; Arnold Welch lecture, Yale University, and the Hodge lecture, Rochester University. He was invited to participate in a Ciba symposium, London. He also received the Nobel Prize in Medicine or Physiology, and an Honorary LLD, George Washington University. He has been invited to join the Psychopharmacology Study Section, NIMH.

Publications:

Black, I.B. and Axelrod, J.: Inhibition of tyrosine transaminase activity by norepinephrine. J. Biol. Chem. 244: 6124-6129, 1969.

Axelrod, J.: Comparative biochemistry of the pineal gland. Am. Zoologist 10: 259-267, 1970.

Axelrod, J.: The pineal gland. Endeavour 29:144-148. 1970.

Axelrod, J.: Amphetamine: metabolism, physiological disposition and its effects on catecholamine storage. In: Costa E. and Garattini S. (Eds.): Amphetamines and Related Compounds. New York City, Raven Press, 1970, pp 207-216.

Axelrod, J., Mueller, R.A., and Thoenen, H.: Neuronal and hormonal control of tyrosine hydroxylase and phenylethanolamine N-methyltransferase activity. In: SchÜmann, H.J. and Kroneberg, G. (Eds.): Bayer Symposium II, New Aspects of Storage and Release Mechanisms of Catecholamines. Heidelberg, Springer-Verlag, 1970, pp 212-219.

Black, I.B. and Axelrod, J.: Biphasic effect of norepinephrine in the regulation of hepatic tyrosine transaminase activity. Arch. Biochem. Biophys. 138: 614-619, 1970.

Black, I.B. and Axelrod, J.: The regulation of some biochemical circadian rhythms. In: Litwack, G. (Ed.): Biochemical Actions of Hormones, New York City, Academic Press, Inc., 1970, Vol. 1 pp 135-155.

Cohn, C.K., Dunner, D.L., and Axelrod, J.: Reduced catechol-O-methyltransferase activity in red blood cells of women with primary affective disorder. Science 170: 1323-1324, 1970.

Lemberger, L., Silberstein, S.D., Axelrod, J., and Kopin, I.J.: Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. Science 170: 1320-1322, 1970.

Molinoff, P.B., Brimijoin, S., Weinshilboum, R., and Axelrod, J.: Neurally mediated increase in dopamine-β-hydrosylase activity. Proc. Natl. Acad. Sci. 66:453-458, 1970.

Mueller, R.A., Thoenen, H., and Axelrod, J.: Effect of pituitary and ACTH on the maintenance of basal tyrosine hydroxylase activity in the rat adrenal gland. Endocrinology 86: 751-755, 1970.

Mueller, R.A., Thoenen, H., and Axelrod, J.: Inhibition of neuronally induced tyrosine hydroxylase by nicotinic receptor blockade. Europ. J. Pharmacol.10: 51-56, 1970.

Tamarkin, N.R. Goodwin, F.K., and Axelrod, J.: Rapid elevation of biogenic amine metabolites in human CSF following probenecid. Life Sci. 9: 1397-1408, 1970.

Thoenen, H., Mueller, R.A., and Axelrod, J.: Neuronally dependent induction of adrenal phenylethanolamine-N-methyltransferase by 6-hydroxydopamine. Biochem. Pharmacol. 19: 669-673, 1970.

Weinshilboum, R. and Axelrod, J.: Dopamine-β-hydroxylase activity in the rat after hypophysectomy. Endocrinology 87: 894-899, 1970.

Axelrod, J., and Cohn, C.K.: Methyltransferase enzymes in red blood cells. J. Pharmacol. Exp. Ther. 176:650-654, 1971.

Black, I.B. and Reis, D.J.: Cholinergic regulation of hepatic tyrosine transaminase activity. J. Physiol./London 213:421-433, 1971.

Weinshilboum, R. and Axelrod, J.: Serum dopamine-β-hydroxylase activity. Circulation Res. 28: 307, 1971.

Serial No. M-CS-ET-1
1. Laboratory of Clinical Science
2. Section on Experimental Therapeutics
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biochemistry, Pharmacology and Physiology of Cerebral Amines

Previous Serial Number: M-CS-OC(C)-14

Principal Investigator: Thomas N. Chase

Other Investigators: Robert W. Colburn, Edna K. Gordon, Irwin J. Kopin, Larry Keng-Yong Ng (Guest Worker) and August M. Watanabe

Cooperating Units: Office of the Chief, Laboratory of Clinical Science, NIMH

Man Years:		
	Total	1.5
	Professional	1.0
	Other	0.5

Project Description:

Objectives: To study the transport, metabolism, release and postsynaptic interactions of biogenic amines and other putative central neurotransmitters and the manner in which these processes are modified by drugs, electrolytes and nerve terminal depolarization.

Methods Employed:

1. Slices or homogenates of brain and other tissues are incubated with radioactively labeled amines and related compounds, then exposed to drugs, other amines or electrical stimulation.

2. Labeled amines and other substances are injected intravenously or intracranially and the concentration of labeled compounds in brain, cerebrospinal fluid, serum and urine determined under various experimental conditions.

Major Findings: Experiments carried out with L.K.Y. Ng, R.W. Colburn and I.J. Kopin have shown that L-dopa stimulates the efflux of labeled dopamine or serotonin from rat brain slices. This action appeared dependent upon the decarboxylation of L-dopa to dopamine, since it could be blocked by an inhibitor of dopa decarboxylase. The selective destruction of catecholamine-containing nerve terminals with 6-hydroxydopamine decreased the uptake and release of labeled dopamine, but not that of labeled serotonin. These observations suggest that exogenously administered L-dopa may enter central serotonergic terminals, undergo decarboxylation to the amine and subsequently be released during nerve terminal depolarization. This mechanism may be relevant to the therapeutic or side effects of L-dopa in parkinsonian patients and might explain why seriously

affected patients, in whom there is a marked loss of dopaminergic neurons, respond as well to L-dopa as those who have only mild disease.

Studies of the effect of conventional antiparkinsonian drugs on the uptake and metabolism of dopamine in rat brain have continued in collaboration with Dr. L.K.Y. Ng. Available results indicate that several of these agents block dopamine uptake into cerebral tissues and accelerate the synthesis of dopamine from systemically administered tyrosine.

An investigation of the effect of systemically administered L-dopa on the metabolism and release of serotonin in mammalian brain has been undertaken in collaboration with L.K.Y. Ng and A.M. Watanabe using dogs with chronically implanted intraventricular needle guides.

Previously developed methods for determining labeled acetylcholine and choline have been employed in preliminary experiments to examine the effects on central cholinergic mechanisms of drugs such as phenothiazines and tricyclic antidepressants, which are known to influence central monoamines.

The ability of low concentrations of various monoamines to release other monoamines from slices or homogenates of brain tissue has been explored. Preliminary results suggest that dopamine releases serotonin and vice versa by mechanisms other than stoichiometric displacement from central storage sites.

Significance to Biomedical Research and the Program of the Institute: Studies of central biogenic amines may help elucidate their role in normal and disordered brain function, and assist in the rational development of improved agents for the treatment of neuropsychiatric disease.

Proposed Course of Project: Current studies of the effects of L-dopa, apomorphine, haloperidol and other centrally active drugs on central monoaminergic transmission will be continued. New experiments to evaluate the presynaptic effects of monoamines in brain and the functional interrelationship between monoaminergic and cholinergic neuronal systems in brain are planned.

Honors and Awards: Dr. L.K.Y. Ng was awarded the S. Weir Mitchell prize by the American Academy of Neurology, April 1971.

Publications:

Chase, T.N., Katz, R.I., Kopin, I.J.: Effect of Diazepam on fate of intracisternally injected serotonin-C^{14}. J. Neuropharm. 9:103-108, 1970.

Ng, K.Y., Chase, T.N., Colburn, R.W., Kopin, I.J.: L-dopa-induced release of cerebral monoamines. Science 170:76-77, 1970.

Ng, K.Y., Chase, T.N., Kopin, I.J.: Drug-induced release of norepinephrine-^{3}H and serotonin-^{3}H from brain slices. Nature 228:468-469, 1970.

Katz, R.I., Chase, T.N.: Neurohumoral mechanisms in the brain slice. Adv. Pharmacol. Chemotherap. 8:1-30, 1970.

Chase, T.N., Breese, G.R., Gordon, E.K., Kopin, I.J.: Catecholamine metabolism in the dog: Comparison of intravenously and intraventricularly administered [^{14}C]dopamine and [^{3}H]norepinephrine. J. Neurochem. 18:135-140, 1971.

Ng, K.Y., Chase, T.N., Colburn, R.W., Kopin, I.J.: Dopamine: Stimulation-induced release from central neurons. Science 172: 1971.

Serial No. M-CS-ET-2
1. Laboratory of Clinical Science
2. Section on Experimental Therapeutics
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Clinical Studies of Cerebral Amines

Previous Serial Number: M-CS-OC(C)-15

Principal Investigator: Thomas N. Chase

Other Investigators: Jacob A. Brody, Edward F. Donnelly, Roswell Eldridge, W. King Engel, Edna K. Gordon, Ira T. Lott, Irwin J. Kopin, Jerry R. Mendell, Dennis L. Murphy, Larry K.Y. Ng (Guest Worker), James A. Schnur, August M. Watanabe and Richard Wyatt

Cooperating Units: Laboratory of Psychology, Laboratory of Clinical Psychobiology and Adult Psychiatry Branch, NIMH; Epidemiology Branch and Neurology Branch, NINDS; Children's Diagnostic and Study Branch, NICHD; Office of the Chief and Section on Psychiatry, Laboratory of Clinical Science, NIMH

Man Years:

Total	1.5
Professional	1.0
Other	0.5

Project Description:

Objectives:

1. To examine the role of biogenic amines in the central nervous system of normal subjects and in patients manifesting neuropsychiatric disease.

2. To test the therapeutic efficacy of amine active drugs in patients with disorders of central nervous system function.

3. To study the central metabolism, transport and mechanisms of action of pharmacologic agents which influence brain amines and other putative neurotransmitters.

Methods Employed: Longitudinal studies are conducted to correlate (a) clinical state as determined by neurologic, psychiatric and psychological examination, (b) metabolism and transport of cerebral biogenic amines through determination of endogenous amines and their derivatives in cerebrospinal fluid, blood and urine, as well as through assay of radioactively labeled substances following intravenous or intracerebral administration of their precursors, (c) spontaneous and evoked cortical electrical activity during waking and sleep and (d) effect of drugs known to influence biogenic amines in brain.

Major Findings: Studies of monoamine catabolites in the cerebrospinal fluid of patients receiving probenecid have provided considerable information on the relationship between the dynamic state of cerebral monoamines and clinical signs of brain dysfunction. Probenecid interferes with the transport from central nervous system of homovanillic acid, a principle catabolite of dopamine, and 5-hydroxyindoleacetic acid, the major product of serotonin degradation. The rate of accumulation of these organic acids in spinal fluid during probenecid administration thus yields an index of their rate of formation as well as of the central turnover of the parent amine. A study conducted with the Epidemiology Branch, NINDS, revealed a marked diminution in the probenecid-induced accumulation of homovanillic acid and 5-hydroxyindoleacetic acid in the spinal fluid of Guamanian patients with parkinsonism-dementia or amyotrophic lateral sclerosis. Probenecid tests carried out in this country in patients with Parkinson's disease have demonstrated a similar reduction in central dopamine turnover. Parallel studies conducted with the Neurology Branch, NINDS revealed a significant decrease in the probenecid-induced accumulation of homovanillic acid in the spinal fluid of amyotrophic lateral sclerosis patients (Mendell, Chase and Engel; Trans. Amer. Neurol. Assn.). The findings in amyotrophic lateral sclerosis patients both here and in Guam are of interest since the disorder is not thought to involve central neuronal systems which contain dopamine. Probenecid studies in patients with Down's syndrome carried out with Drs. Ira Lott and Dennis Murphy, failed to demonstrate any alteration in the turnover of central monoamines despite the finding that platelet levels of serotonin were markedly diminished due to a defect in uptake mechanisms. The results suggest that the platelet may not serve as a useful model of central neurons with respect to the transport and metabolism of monoamines. Probenecid tests carried out in patients with Huntington's chorea and dystonia musculorum deformans failed to disclose any abnormality in central monoamine turnover.

Probenecid studies have also contributed to our understanding of the effect of drugs on brain amines. Haloperidol significantly increased the probenecid-induced accumulation in spinal fluid of homovanillic acid but not 5-hydroxy-indoleacetic acid. This finding is consistent with reports of animal studies showing that haloperidol and related psychotherapeutic agents accelerate central dopamine turnover. Preliminary results in patients receiving tricyclic antidepressants and conventional antiparkinsonian agents, both thought to act centrally by diminishing the reuptake of monoamines released into the synaptic cleft, suggest that an alteration in the turnover of serotonin or dopamine, respectively, attends the administration of these agents in man as in the experimental animal.

Homovanillic acid levels in the spinal fluid of parkinsonian patients receiving therapeutic dose levels of L-dopa alone were twice those occurring in the same patients receiving optimal dose levels of L-dopa in combination with methyl-dopahydrazine. These findings suggest that at least half the homovanillic acid content of human cerebrospinal fluid derives from L-dopa metabolism at sites not participating in the therapeutic effects of L-dopa and may in part explain the lack of correlation between alterations in cerebrospinal fluid levels of homovanillic acid and the response of parkinsonian patients to L-dopa.

Studies of monoamine metabolite levels in the cerebrospinal fluid of 6 patients receiving brief intravenous infusions of L-dopa carried out with Dr. L.K.Y. Ng indicate that the dopamine precursor releases serotonin and norepinephrine from central stores. Chronic L-dopa administration failed however, to alter the probenecid-induced rise in 5-hydroxyindoleacetic acid suggesting that serotonin turnover in the central nervous system is not substantially altered by long term L-dopa treatment.

A single blind, cross-over study was completed in 14 parkinsonian patients to compare biochemical and clinical effects of L-dopa alone, and in combination with α-methyldopahydrazine, an extracerebral inhibitor of aromatic L-amino acid decarboxylase. Use of the decarboxylase inhibitor reduced the optimal therapeutic dose of L-dopa by 76%. At maintenance dose levels of L-dopa, given alone or with methyldopahydrazine, neurologic improvement averaged about 65%. Combination therapy substantially diminished the incidence of L-dopa induced vomiting and thus permitted a marked acceleration in the rate at which the L-dopa dose could be increased to maintenance levels. Centrally mediated side effects of L-dopa such as hypotension, dyskinesia, and behavioral changes were not altered by concomitant use of methyldopahydrazine. No toxic effects attributable to α-methyldopahydrazine alone or together with L-dopa were observed in the parkinsonian group or in an additional group of 17 neurologic patients receiving this drug combination.

Therapeutic trials of L-dopa in brain disorders other than idiopathic Parkinson's disease have continued. In a study carried out with the Epidemiology Branch, NINDS, L-dopa was found to substantially ameliorate extrapyramidal function in 8 Guamanians with parkinsonism-dementia (Schnur, Chase, and Brody; Neurology). Associated dementia failed to improve. In another study carried out with the Neurology Branch, NINDS, L-dopa was administered to 10 Americans with amyotrophic lateral sclerosis (Mendell, Chase and Engel; Arch. Neurol.). Despite spinal fluid findings suggesting that dopamine turnover is reduced in patients with this disorder, L-dopa failed to benefit motor function. It would appear that defects in central dopamine metabolism, as inferred from tests applicable to the living patient, may attend neurologic disorders which are unresponsive to precursor loading with L-dopa.

The effect of amine active drugs on phenothiazine-induced extrapyramidal disorders has now been studied in 4 patients. L-dopa, the immediate precursor of dopamine, reduced parkinsonian signs but exacerbated oral dyskinesias, while α-methylparatyrosine, an inhibitor of dopamine synthesis, produced the opposite clinical results. These observations support the hypothesis that a reduction in functionally available dopamine favors the development of parkinsonian hypokinesia and rigidity, while an excess of this monoamine promotes hyperkinetic-hypotonic states.

5-hydroxytryptophan, the immediate precursor of serotonin, has been administered in combination with methyldopahydrazine to 7 patients with Parkinson's disease. Akinesia and rigidity were increased while tremor remained essentially unchanged. Since 5-hydroxytryptophan competes with L-dopa for uptake, metabolism and

storage centrally, it is likely that the response to 5-hydroxytryptophan is a consequence of reduced dopamine stores at extrapyramidal centers. On the other hand, it is conceivable that serotoninergic and dopaminergic systems act in diametric oppostion with respect to the control of some extrapyramidal functions.

An evaluation of the effect of L-dopa on sleep carried out with Dr. Richard J. Wyatt was completed in 7 patients with various neurologic disorders (Wyatt, Chase, Scott, et al., Nature 228:999, 1970). L-dopa, in doses sufficient to modify extrapyramidal function, produced a significant reduction in REM sleep time. The duration of NREM sleep was not affected.

Psychometric studies in patients receiving amine active drugs continue in collaboration with Dr. Edward F. Donnelly. The administration of L-dopa to 18 patients with various neurologic disorders was associated with an increase in performance IQ scores but no change in verbal IQ scores. Although there was a tendency for subtest results on the Wechsler Adult Intelligence Scale to increase during L-dopa treatment, scores on the comprehension subtest, which measures common sense judgment, declined significantly. Collateral evidence supports the contention that L-dopa may influence this aspect of human cognitive function.

Significance to Biomedical Research and the Program of the Institute: Biogenic amines appear to act as synaptic mediators in certain neuronal systems within the central nervous system of man. Alterations in these substances have been found in relation to several extrapyramidal disorders and have led to trials of drugs which reverse both the biochemical and neurologic defects. This approach to the development of new drug therapies may be applicable to other disorders of central nervous system function.

Proposed Course of Project: Current studies of monoamine metabolism and transport in relation to neuropsychiatric disease will be continued. A major effort will be directed towards the development of improved techniques for evaluating central monoaminergic function in man. Attempts to modify psychomotor function with drugs known to possess specific actions on central monoamines will be extended.

Honors and Awards:

Dr. Chase was invited to serve on the executive Editorial Board of Neuropharmacology. He was asked to join the World Federation of Neurology Research Group on Huntington's Chorea and to serve on the program committee for The George Huntington Commemorative Symposium to be held in Ohio in March 1972. Dr. Chase was also elected to membership in the American Society for Neurochemistry. In addition, Dr. Chase was an invited participant in a Workshop on Huntington's Chorea sponsored by the Committee to Combat Huntington's Disease held in Los Angeles, March 12-13, 1971 and at the third annual meeting of collaborative investigators for studies of Levodopa in Parkinson's Disease held in Nutley, New Jersey, June 17, 1971 and to chair a panel on "Dopa Metabolism" at the Second Annual Symposium on Pharmacologic and Clinical Experiences with Levodopa, Georgetown University, April 26, 1971. Dr. Chase served as an invited discussant for papers entitled, "Treatment of Parkinson's Disease with Levodopa alone or

with RO4-4602" and "Release of brain norepinephrine into the ventricle by hypothalamic stimulation in the cat" presented to the American Academy of Neurology, New York City, April 29-May 1, 1971. Invitational lectures and seminars presented by Dr. Chase during the past year included: "Drug-induced extrapyramidal disorders" to the Association for Research in Nervous and Mental Disease in New York City, December 4-5, 1970; "Monoamine Studies in Huntington's Disease" to the World Federation of Neurology Research Group on Huntington's Chorea, Munich, Germany, August 29-September 3, 1970.

Publications:

Chase, T.N., Schnur, J.A. and Gordon, E.K.: Cerebrospinal fluid monoamine catabolites in drug-induced extrapyramidal disorders. Neuropharm. 9:265-268, 1970.

Chase, T.N.: Biochemical and pharmacologic studies of dystonia. Neurology 20 (Part 2):122-130, 1970.

Chase, T.N.: 5-hydroxtryptophan in parkinsonism. Lancet ii:1029-1030, 1970.

Chase, T.N.: Cerebrospinal fluid monoamine metabolites and peripheral decarboxylase inhibitors in parkinsonism. Neurology 20 (Part 2):36-40, 1970.

Serial No. M-P-C-(C)-12
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies of heredity and environment in schizophrenia.

Previous Serial Number: Same.

Principal Investigator: David Rosenthal

Other Investigators: Paul H. Wender, Seymour S. Kety (Harvard), Shmuel Nagler (Israel), Fini Schulsinger (Denmark)

Cooperating Units: Laboratory of Clinical Science; 4 West, 3 East Clinical Center Wards.

Man Years:

Total:	4.0
Professional:	2.5
Other:	1.5

Project Description:

Objectives: To understand how hereditary and environmental factors interact to make for schizophrenic outcomes of varying types and degrees.

Methods Employed: 1. A constructively critical, hypothesis-oriented analysis of the worthwhile literature on heredity and environment in schizophrenia. 2. An intensive multidisciplinary study of a family with one-egg quadruplet daughters concordant as to schizophrenia but discordant as to severity and outcome. This study was published in book form. We are continuing our contacts with this family to see what happens in the clinical course of these girls and how the course is related to earlier and current life experiences. 3. Studies of adoptees and their biological and adoptive families. 4. A study of children (of schizophrenic and control parents) reared in town or kibbutz in Israel.

Major Findings: 1. The analysis of the literature has been reported in a series of papers and in the study of the quadruplets. A textbook which organizes and explicates the literature on the genetics of behavioral disorders was published last year, and a modified version of this book was published this year. 2. Several papers on our adoption studies are now published. The studies indicate that hereditary factors contribute to the development of schizophrenia, and to other disorders that we include in a group called the schizophrenic spectrum. Several articles are in preparation and eventually

a monograph will be written on the adoption studies. Data analysis is continuing. 3. One hundred subjects in the Israel study have been examined, and the research findings are currently being analyzed and evaluated. Preliminary findings indicate that offspring of schizophrenics have more neuropathological signs in childhood than do controls. Two subjects have had a breakdown and one is on the verge of breakdown. All three have a schizophrenic parent.

Significance to Bio-medical Research and the Program of the Institute: We have resolved a chronic, critical problem in psychiatry by demonstrating beyond any reasonable doubt that genetic factors are importantly involved in the etiology of schizophrenia and related mental disorders. Moreover, the evidence thus far suggests that the mode of genetic transmission is polygenic or a dominant single gene with polygenic modifiers.

Proposed Course of Project: We are examining additional subjects in Denmark with the following goals in mind: 1. to try to discriminate gene carriers and non-gene carriers with respect to personality and test variables; 2. to compare the fate of gene-carriers who are reared in the parental home as compared to those reared in adoptive homes; 3. to compare Ss who have a psychotic biological parent but who are reared by nonpsychotics with Ss whose biological parents are not psychotic but who are reared by a psychotic adoptive parent; 4. to find the incidence of schizophrenic spectrum disorder in a random sample of the Danish population. In Israel, our goal is to prepare a volume on our findings and their theoretical implications. During this year we were granted support to carry out a three-year follow-up study of this unique sample of subjects.

Honors and Awards:

Member, Advisory Board, Behavior Genetics
Referee, Social Biology
Editorial Consultant, Schizophrenia Bulletin, NIMH
Member, Review Panel, Clinical Research Review Committee, NCMHSTR, NIMH
Ninth Annual Stanley R. Dean Research Award "to a scientist or a group of scientists who have made a major contribution to basic research in the behavioral sciences relevant to schizophrenia."
Outstanding Contribution Award, by Maryland Psychological Ass. for 1971.

Publications:

Wender, P. H., Rosenthal, D. and Kety, S. S.: A psychiatric evaluation of the adoptive parents of schizophrenic patients. (Proceedings of the IV World Congress of Psychiatry, Madrid, 5-11 September, 1966.) Excerpta Medica International Congress Series No. 150, Part 2, 1968, 1103-1106.

Rosenthal, D.: Familial Concordance by Sex with Respect to Schizophrenia. In D. N. Robinson (Ed.), Heredity and Achievement. New York, N. Y.: Oxford University Press, 1970, Pp. 137-170.

Rosenthal, D., and Van Dyke, J.: The use of monozygotic twins discordant as to schizophrenia in the search for an inherited characterological defect. In Stromgren, E. (Ed.), Studies Dedicated to Erik Essen-Moller, Copenhagen: Munksgaard. Acta Psychiatrica Scandinavica 46: Suppl. 219, 183-189, 1970.

Rosenthal, D. Genetics of Psychopathology. New York: McGraw-Hill, 1971, 183 pp.

Rosenthal, D. Two adoption studies of heredity in the schizophrenic disorders. In Bleuler, M., and Angst, J. (Eds.), The Origin of Schizophrenia, Bern: Verlag Hans Huber, 1971, pp. 21-34.

Serial No. M-P-C-(C)- 15
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Reaction time in schizophrenia.

Previous Serial Number: Same

Principal Investigator: Theodore P. Zahn

Other Investigators: Paul Fedio, Larry Ng

Cooperating Units: Surgical Neurology Branch, NINDS
Laboratory of Clinical Science, NIMH

Man Years:

Total:	.2
Professional:	.1
Other	.1

Project Description:

Objectives: To study deficits in attention in schizophrenia, particularly as manifested in difficulties in adopting and maintaining preparatory sets. To discover methods of improving these. To study the specificity of such deficits to schizophrenia. To study possible organic and genetic determinants of such deficits.

Methods Employed: (A) A reaction time (RT) technique which puts severe demands on attention and which discriminates well between schizophrenic and non-schizophrenic subjects is being given to patients before and after unilateral temporal lobectomy for the relief of psychomotor epilepsy. This procedure and a choice technique which compared RT to monaural stimulation in each ear and responses with the same or opposite hand have also been used on postoperative temporal lobe followup cases and normal controls.

(B) Two studies have attempted to improve the reaction time (RT) performance of chronic schizophrenics by manipulations of the experimental conditions. Previous research from this laboratory and elsewhere has shown schizophrenics to have a disproportionate deficit in simple RT on trials having short preparatory intervals (PI) when these trials are mixed randomly with longer PI trials. We attempted to determine if this was due to a faulty pattern of expectancies or to errors in time estimation by informing the subjects, under one condition, whether the next trial was going to have a short or a long PI.

(C) The basic RT procedure is also being used in a double-blind design on a series of narcoleptic patients in conjunction with a trial of L-dopa as a possible therapeutic agent.

Major Findings: A. We continue to find that about half of the temporal lobe followup cases give essentially normal performance despite some apparent personality disturbance. Most patients tested 10-15 days post-operatively have shown a decline from their preoperative performance level, suggesting a possible recovery of function over time. The followup cases are also slower in choice RT but further analysis of the data is needed to determine if this slowing is disproportionate to the simple RT level.

B. Pretrial information about the PI significantly improved the RT of schizophrenics in each of two experiments on the shorter of the two PIs used, but the improvement was less, in proportion to the total deficit under these conditions, than was given by groups of normal subjects. An analogous procedure using choice RT (to rule out time estimation as a factor) produced similar results. Thus neither faulty expectancies nor time estimation errors seem to be the critical factors in this deficit. Rather, schizophrenics seem unable to utilize or act on information in order to prepare in advance for the stimulus.

C. In four narcoleptic patients it was found that reaction time impairment occurred sporadically--on some trials but not on others. Treatment with L-dopa initially improves performance but there seems to be a tolerance to the effects of the drug over time. These results agree quite well with clinical findings, suggesting that the reaction time test is a sensitive and objective indicator of the clinical course of this illness.

Significance to Biomedical Research and the Program of the Institute: These studies are designed in part to explore the possibility of a biological basis for schizophrenia. Since patients with lesions in the temporal lobe frequently exhibit a schizophrenic-like personality picture and since patients with other types of brain lesions have been found to exhibit reaction time deficits (but of different types than those shown by schizophrenics) the reaction time performance of these patients might indicate if a temporal lobe disturbance is possibly involved in schizophrenia. The reaction time studies with schizophrenics add to our knowledge of the specific psychological processes involved in the disorders of set and attention that seem to be important aspects of the schizophrenic process.

Proposed Course of Project: Further collection of data on both current and followup temporal lobe cases. When enough data have been collected the effects of the side of the lesion and correlations with the amount of tissue removed can be determined.

Honors and Awards: None.

Publications:

Zahn, T. P. Effects of reductions in uncertainty on reaction time in schizophrenic and normal subjects. J. exp. Research in Pers. 4: 135-143, 1970.

Serial No. M-P-C-(C)- 17
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychophysiological Responsivity in Schizophrenia

Previous Serial Number: Same

Principal Investigator: Theodore P. Zahn

Other Investigators: David Rosenthal, William Pollin, Loren Mosher

Cooperating Units: Adult Psychiatry Branch, NIMH
Clinical Research Branch, ERP-HSMHA-NIMH

Man Years:

Total:	1.2
Professional:	.9
Other	.2

Project Description:

Objectives: The general purpose of these studies is to investigate schizophrenic-normal differences in the relative autonomic responsivity to various stimuli, the relationship of autonomic activity to adequacy of performance and to psychiatric condition, and possible genetic determinants. Studies of brain mechanisms and other physiological mechanisms involved in autonomic activity are also in progress.

Methods Employed: 1. Peripheral measures of autonomic functioning, namely GSR, heart rate, finger pulse volume, respiration and skin temperature are recorded during several sessions in which stimuli are presented and tasks are performed which vary in the demands placed on the subjects: no stimuli, simple auditory stimuli with no response required, the same with a "casual" response required, reaction time, word association, mental arithmetic, and cold presser. Specific and non-specific response frequencies and amplitudes, baseline values and baseline changes are measured. These procedures have been used with identical twins discordant or concordant for schizophrenia and their parents and with the adoptive and biological parents of schizophrenic patients in order to see if whatever genetic influence there is in schizophrenia is manifested in autonomic functioning.

Methods have been developed in our laboratory to analyze skin conductance, heart rate, skin temperature and finger pulse volume data automatically from taped analog records by means of the LINC computer.

More refined methods are being developed on the SEL 810B computer. Further analyses are being carried out on the IBM 360 and the CDC 3100 computers.

2. A large scale exploratory correlational analysis using both univariate and multivariate (canonical) correlations of the psychophysiological variables with biochemical and psychiatric data collected by other investigators is being carried out to determine the interrelationships between these major classes of variables.

3. Analyses of the genetic determinants of psychophysiological variables on the data from the twins is being carried out by a method of intra-class correlation which attempts to control for any consistent influence of psychopathology on the dependent variable.

4. The variability in psychophysiological functioning is of increasing interest to investigators in this field as possibly reflecting the operation of regulating mechanisms. In addition to measuring the magnitude of spontaneous electrodermal and heart rate fluctuations, analyses of the frequencies of heart rate variations have been done by computing power spectra on the autocorrelation functions. Methods are being developed to compare individual subjects with respect to the patterns of frequencies exhibited. Since examination of the autocorrelations suggest an autoregressive process, methods are being developed to fit an autoregressive model to the data for individual subjects.

5. Skin conductance data from several studies are being reanalyzed using a "range corrected" measure by which it is hoped to remove some of the extraneous variation due to anatomical factors from this measure.

6. A large series of Mz and Dz normal twins are being tested on a briefer version of the above procedures in order to determine the relative importance of genetic and non-genetic factors in psychophysiological functioning. These data will also be compared with electroencephalographic, perceptual and personality data collected by other investigators.

7. A series of minimally brain damaged children are being tested with our procedures in conjunction with a clinical trial of lithium.

Major Findings: 1. Previously we had found that the differences between the schizophrenic and non-schizophrenic members of the twin pairs were similar to the differences between unrelated schizophrenic and normal subjects in that: (a) despite equal autonomic responsivity to meaningless stimuli, the schizophrenics were significantly hyporeactive to more meaningful stimuli; and (b) the schizophrenics showed higher arousal levels under nondemanding conditions but the controls showed a greater increase in arousal under the mild stress of task performance.

2. Preliminary results from the correlational analyses show unexpected but consistent negative correlations between electrodermal and

heart rate indices of arousal and urinary measures of the precursors and metabolites of epinephrine and norepinephrine (dopamine, metanephrine, and normetanephrine). In addition perinatal birth complications (PBC) seem to play a role: index cases with a higher number of PBC than their control twin are lower in the norepinephrine series and higher in skin conductance measures of arousal in relation to their control twins as compared with those index cases who had an equal or lower number of PBC.

3. Preliminary analyses of the genetic determination of psychophysiological variables has shown that overall autonomic arousal levels, variability and responsivity seem to have a significant genetic-familial component, while performance measures and the autonomic response to demand do not show appreciable genetic influence.

4. Most subjects show significant heart rate fluctuations occuring at 4-8 cycles per minute in addition to sinus arrhythmia (15 - 20 cycles per minute). Some of the twin pairs show strikingly similar spectra.

5. A review of the literature on the relationships of autonomic phenomena to behavior in schizophrenia has revealed much support for the implication from our research that there is no generalized deficit in autonomic reactivity in schizophrenia, but that such deficits occur specifically to meaningful or demanding stimuli such as those involved in task performance. It is also apparent from the literature that a simple inverted-U relation between autonomic arousal and performance is not well confirmed, and that what we have called specific and non-specific arousal might have different relationships to behavior in schizophrenia.

Significance to Biomedical Research and the Program of the Institute: The role of autonomic arousal and responsivity in schizophrenic deficits in behavior remains obscure, but it is clear from our own research and that of other investigators that a low arousal level is not the critical factor as has sometimes been postulated. Our evidence suggests that a high arousal level that is non-task-related (non-specific arousal) and low task-related increments in arousal or the relationship between these may be related to such performance deficits. Further elucidation of the autonomic concomitants of behavior deficits in schizophrenia may give us an increased understanding of the biological aspects of this condition and therefore may lead to more specific therapeutic procedures.

In view of the abundant evidence that genetic factors are of importance in the etiology of schizophrenia, it is reasonable to ask if a "schizophrenic genotype" is manifested in the autonomic nervous system. Such involvement seems even more likely on the basis of reports that children who later develop psychiatric illnesses presumably due to a combination of genetic constitution and PBC have characteristic autonomic patterns before the onset of the symptoms. The study of normal twins is designed to determine which aspects of autonomic functioning are influenced by genetic factors. This knowledge should help to determine the mechanisms of the autonomic patterns

seen in individuals with a presumed schizoid genotype.

Proposed Course of Project:/ 1. Further analysis of the data from the twins and their families will include (a) examining more autonomic variables such as vasomotor changes, and other aspects of electrodermal functioning based on new findings in the literature; (b) multivariate statistical analysis of group differences; and (c) partial correlations on selected subsets of the large set of variables from different investigators. 2. The development of techniques to manipulate general arousal levels and specific alerting systems independently. The use of shock to reinforce slow reaction times and in a non-contingent fashion may be a promising start on this problem. 3. More precise measurement of cardiac responsivity will be attempted by means of estimation techniques based on autoregressive and crossregressive models of heart rate variation.

Honors and Awards: None.

Publications:

Zahn, T. P. Psychophysiological concomitants of task performance in schizophrenia. In: Zubin, J., Sutton, S. and Kietzman, M.L. (Eds.), Objective Indicators of Psychopathology, Academic Press, New York, 1971.

Wender, P. H. Rosenthal, D., Zahn, T. P., and Kety, S.S. The psychiatric adjustment of the adopting parents of schizophrenics. Am. J. Psychiat. 127: 1013-1018, 1971.

Serial No. M-P-C-(C)- 36
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychological Correlates of Cortical Evoked Responses

Previous Serial Number: Same

Principal Investigator: Monte Buchsbaum

Other Investigators: Adolf Pfefferbaum, Lyman C. Wynne, Paul Fedio, Dennis Murphy, Frederick Goodwin, George M. Henry, and Paul H. Wender.

Cooperating Units: Adult Psychiatry Branch, NIMH
Surgical Neurology Branch, NINDS
Laboratory of Clinical Science, NIMH

Man Years:

Total:	2.2
Professional:	1.2
Other:	1.0

Project Description:

Objectives: Exploration of relationships between perceptual response patterns, psychiatric clinical dimensions and neurophysiological measures; the development of neurophysiological tests which may be useful in further understanding perception; the adaptation of neurophysiological procedures for assisting in the selection of therapeutic drugs or other techniques for aiding in the diagnostic and etiological categorization of psychiatric patients.

Methods Employed: Research in this project focuses on the automatic and electrophysiological correlates of perceptual, cognitive and motor behavior in normal and psychiatrically disturbed human subjects. We approach psychiatric disabilities by studying perceptual style--the way in which each individual shapes, alters, and attends to sensory stimuli in his environment. To what extent unusual perceptual function represents etiological, symptomatic, or even restorative aspects of mental illness is unclear, and it is to the effort to better understand this relationship that our research is directed.

Central nervous system function has been difficult to study in psychiatric patients by either conventional neuroanatomic or implanted electrode techniques, as the former requires a dead patient (or an animal

model of the disease) and the latter requires a hazardous surgical procedure. Obviously, neither method permits long-term study of psychiatric episodes. With the development of average evoked response techniques, which allow recovery of relatively specific CNS signals from scalp EEG, neurophysiological attempts to study psychiatric disorders received new impetus. The average evoked response (AER) is a particularly promising tool for studying perception in the psychiatric patient because, unlike traditional psychophysical techniques, it does not depend upon the patient's report or overt performance. Thus, the importance of motivation or motor activity is minimized and a clearer separation of perceptual (input) and performance (output) factors may be achieved.

Cortical average evoked responses (AER's) are patterns of electrical response to sensory input which are recorded from the electroencephalogram. Because evoked responses are usually of extremely small amplitude (less than 10 millionths of a volt), these patterns are completely lost in the apparently random fluctuation of the EEG. But we can overcome this obstacle by taking advantage of the fact that an evoked response is always related in time, or "time-locked," to a sensory stimulus, whereas the background EEG activity varies and bears no fixed relationship to the stimulus. By presenting the subject with a long series of stimuli, such as flashes of light, and summing the EEG for a brief time interval after each flash, an AER is produced.

The development of computer technology has been an essential step in the application of AER measures to large-scale patient testing. Patients and normal subjects have been studied at the Clinical Center using the LINC and SEL computers, at St. Elizabeths Hospital with the PDP-12 computer and, in collaboration with Dr. George Borge, at the Illinois State Psychiatric Institute with a special purpose averaging computer. To allow collaborating psychiatrists and graduate students to develop their own experiments and run their own subjects we have utilized ERL--an interpretive compiler to construct AER experimental programs from English-language-like commands and CERES--a computer monitor system.

Last year, because of our section's interest in genetic and/or familial factors in schizophrenia and affective disorders, we began a three-phase program to further refine this electrophysiological measure of perceptual functioning as a tool for studies of psychiatric patients and their families. This program has included: 1) methodological studies of the AER and augmenting-reducing; 2) pilot studies of patients with affective disorders and schizophrenia; and 3) studies of perceptual and AER measures in twins.

Major Findings: 1. Methodological. Our finding of wide differences between people on a neurophysiological measure, the AER, led to the development of a perceptual style measure known as "stimulus intensity control." This measure defined two types of individuals who were thought to modulate sensory input differently--the augmenter who tends to increase the perceived intensity of stimuli and the reducer who tends to decrease the perceived intensity of stimuli.

Coping with sensory overload is perhaps a major adaptive problem for 20th century urban man. Therefore it is interesting to speculate whether the reducer's style of "turning off" or "turning down" is a protective process operating to prevent sensory inundation. The reducer's opposite, the "turning on" augmenter, may either lack this protective mechanism or perhaps be a glutton for sensation. These neurophysiological differences are echoed in psychological tests results. On the Zuckerman Stimulus Seeking Questionnaire, for example, reducers scored low on thrill and adventure seeking, whereas augmenters scored high on this factor. Similarly, on the MMPI, augmenters tended to be paranoid and manic, while reducers were depressed and hysterical. In experiments utilizing unpleasant loud noises, reducers shifted toward still more extreme reduction.

2. Patient Studies. Patient studies tend to confirm these differences; manic and paranoid schizophrenic patients tend to augment and depressed and non-paranoid patients tend to reduce. Adolescents with acting-out behavior problems were also greater augmenters than their less disturbed siblings. Hyperactive children both on and off amphetamines are currently under study.

Continuing studies of patients with affective disorders further confirmed the finding that bipolar (manic-depressive) patients showed augmenting whether they were in the manic or depressed phase whereas unipolar (depressed) patients always reduced. Further, the greater the degree of augmentation on baseline days, the greater the probability of successful therapy with lithium. Thus, the separation of depressed bipolar and depressed unipolar patients on the basis of different AER responses is evidence in support of this diagnostic distinction as is their differential responsivity (both clinically and on the AER procedure) to lithium.

3. Twin and Family Studies. Data on AER psychophysiology and perceptual tasks on the first 24 pairs of twins have been collected and data collection will continue for the next year.

Significance to Bio-Medical Research and the Program of the Institute: This project, in helping to give a neurophysiological basis to psychological tests, contributes to the effort to understand mechanisms of variation in human personality. Further, the technique derives psychological information without relying on language or more than passive cooperation from the subjects. Thus, the project attempts to use basic psychophysiological techniques to enhance our understanding of such topical clinical problems as adolescent runaways and the amphetamine treatment of hyperactive children.

Proposed Course of Project. 1) Study of genetic factors in perception using twins will continue. 2) An online infrared TV-computer system for pupillometry has been set up and software developed. Pupil diameter will be measured both as a perceptual style variable related to sensory inundation and in real time AER experiments. 3) The SEL computer system will be developed toward an operational process control--data analysis--statistical summary system. 4)Experiments on the role of attention and augmenting/reducing will be begun.

Honors and Awards: None.

Publications:

Interbitzen, L., and Buchsbaum, M.: The EEG evoked response and perceptual variability in schizophrenia. Arch. Gen. Psychiat. 23: 438-444, 1970.

Buchsbaum, M., and Harris, E.: Diurnal variations in serum and urine electrolytes. J. Appl. Physiol. 30: 27-35, 1971.

Buchsbaum, M., and Henkin, R.: Serum calcium concentration and the average evoked response. Electroenceph. Clin. Neurophysiol. 30: 10-16, 1971.

Pfefferbaum, A., Buchsbaum, M., and Gips, J.: Enhancement of the AER to tone onset and cessation. Psychophysiol. In press.

Buchsbaum, M.: Average evoked response technique and applications. Schiz. Bull. In press. (Winter, 1970).

Buchsbaum, M., Silverman, J., and Henkin, R.: Contrast effects on the auditory evoked response and its relation to psychophysical judgments. Perception and Psychophysics. In press.

Borge, G., Buchsbaum, M., Goodwin, F., Murphy, D., and Silverman, J.: Neuropsychological correlates of affective disorders. Arch. Gen. Psychiat. In press.

Gips, J., Pfefferbaum, A., and Buchsbaum, M.: Use of a small process control computer in a psychophysiological laboratory. Psychophysiol. In press.

Pfefferbaum, A. and Buchsbaum, M. Handedness and cortical hemisphere effects in sine wave stimulated evoked responses. Neuropsychologia. In press.

Gips, J., Pfefferbaum, A. and Buchsbaum, M.: ERL - A language for implementing evoked response and psychophysiological experiments. Behav. Res. Methods and Instrument. In press.

Buchsbaum, M. Neural events and psychophysical law. Science. In press.

Buchsbaum, M. and Pfefferbaum, A. Individual differences in stimulus intensity response. Psychophysiology. In press.

Buchsbaum, M., Goodwin, F., Murphy, D., and Borge, G. AER in affective disorders. Amer. J. of Psychiat. In press.

Fedio, P., and Buchsbaum, M. Unilateral temporal lobectomy and changes in evoked responses during recognition of verbal and non verbal material in the left and right visual fields. Neuropsychologia. In press.

Serial No. M-P-C-(C)-37

1. Laboratory of Psychology
2. Section of the Chief
3. Unit for Research on Behavioral Systems
4. Poolesville

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Environmental and Genetic Variables Affecting Biological Systems

Previous Serial Number: Same

Principal Investigator: John B. Calhoun

Other Investigators: Gerald G. Wheeler, Halsey M. Marsden

Cooperating Units: Section on Pharmacology, CBRS, NIMH
Dr. Julius Axelrod

Man Years

Total:	5.48
Professional:	3.55
Others:	1.93

Project Description:

Objectives: To develop principles relating to complex biological-social systems with particular reference to population growth, social organization and central nervous system function in animals. All comments below will be restricted to the one of the populations of mice from Studies 102 and 103 that was permitted to survive through FY '71. This population, the largest included within this series of studies, has been continued in an effort to determine whether, in population exposed to severe overcrowding, resultant physiological and behavioral pathology precludes any possibility of reproductive or social recovery.

Methods Employed: The experimental and environmental designs remain as described in M-P-C-(C)-37 for FY '70. As a result of this one population increasing to 2200 individuals it became impossible to maintain the initial objectives of recording detailed behavioral histories of each individual. However, on the basis of the considerable life history data we did have on every individual, coupled with an intensive effort to identify all mice who repeatedly exhibited certain quasi-normal or pathological behaviors, 8 groups of males and 8 groups of females with 12 mice in each group were selected for intensive observation. Each of these mice had its fur color coded for individual recognition. 8,000 observations were then made of these 192 select mice. Concurrently with the making of these observations an additional 1,000 observations were made that led to a selection of 16 stressed and 16 unstressed mice of each sex for analysis of enzyme activity in the noradrenalin-adrenalin system.

Major Findings: The cessation of population growth which occurred March 1, 1970 has been followed by a decline in the number of mice from a maximum of 2200 to 1400. During this decline no young survived to weaning and the incidence of pregnancy itself declined to zero. Since even the youngest mice are now approaching menopause, no further recovery of the population is anticipated. Menopause will be reached by all mice by the time normal mortality has reduced the population to 1000, that is to 6 times the optimum number compatible with effective reproduction.

Significance to Bio-medical Research and the Program of the Institute: This current study probably has as broad an implication for mental health as any conducted anywhere on animals. It forms a fitting capstone to the 15 years of research by the principal investigator under the sponsorship of the Laboratory of Psychology which he is leaving at the end of FY '71 to become a member of the newly formed Laboratory of Brain Evolution and Behavior. Adult socially integrated mice have the capacity to nurture, protect, and provide for the behavioral development of only the sufficient number of younger mice necessary to replace themselves in the face of the reduction in their numbers brought about by aging and other mortality factors. Normally many more young are produced than the adults will find necessary to contribute to their behavioral development. These excess young are removed by predators, disease, hunger, inclement weather or emigration. As a result of our elimination of these mortality factors the socially integrated adults found themselves faced with several times the normal number of younger animals moving into adulthood. These subadults had experienced a quite adequate early development-one which provided them with the capacity to compete with their older associates for social roles. Except for a few who were able to replace their older associates, all were rejected - they found no opportunity for expressing their capacity for social involvement. These rejected individuals withdrew physically and psychologically but among themselves became extremely violently

aggressive. None of these social outcasts later became integrated into the established social groups, which continued to reproduce, but less successfully. Young born during this second phase were exposed to a social setting characterized by overcrowding and disruption of the social order. Loss of effective territorial behavior by males led to incursions into each social group's space. Concurrently females who had been good mothers became extremely aggressive. This aggression turned on their own young who were bitten and socially rejected before normal weaning. Furthermore, once these young entered the general social milieu mechanical interference by their many associates often interrupted social interaction sequences of behavior. These two factors, in conjunction with the difficulty of locating another individual in the same state of readiness for interaction when there are so many others, prevented normal behavioral development. Most of the latter two-thirds of the mice born never had the opportunity to develop those critical aggressive, sexual, and maternal behaviors requisite to the survival of the species.

To make a broad generalization: When the adult members of a social system provide adequate early development for more young than they have capacity for providing for their involvement as adults in the established social order, then these excess members will be vigorously rejected. The process of rejection leads to a disruption of capacity for normal social behavior, and culminates in the rejected individual becoming extremely violent, with the violence having its major repercussions turned inward toward other rejected individuals. However, the very process of rejection leads to the disruption of adequate social behavior by the formerly organized adults. Later young reared by them become autistic-like with little capacity to engage in those complex behaviors essential for the survival of the species. These complex behaviors, which in the mouse primarily relate to reproductive and aggressive behavior, on the human level relate to the creation, acquisition and implementation of ideas. The United States and the world stand at a critical stage in evolution having many counterparts to the study of mice. If we fail to make the appropriate adjustments to this mega-crisis the future of the human race is also doomed.

Proposed Course of Project: This last of the large mouse populations will be permitted to continue until all members have died of old age. Three months before the younger animals reached menopause (the day of writing this report) six groups of 4 males and 4 females, judged most likely to be able to recoup normal behavior, were introduced into uncrowded environments. These also will be followed until all have definitely passed menopause to determine if any residual capacity for recovering normal behavior exists.

After five years of development, our project, which involves the computer monitoring of movements and behavior of all members of a group of rats in a structured environment is being placed in operation. Our objective here is to develop a "physics" of social behavior and social organization.

Gradually we have developed the theoretical base and operational capabilities for initiating research on environmental designing, both physical and social. We intend to place increasing emphasis on the environmental conditions which form the mold for guiding the development and expressing of both individual behavior and social organization.

Honors and Awards: (Principal Investigator)

1. Completed 5 years of service as consultant on population to the Committee on Preventive Psychiatry of the Group for the Advancement of Psychiatry.

2. Humanities Seminar Leader at the sessions of the Young Presidents Organization devoted to The Changing Nature of Man, Aspen, Colorado.

3. Consultant to the President of the University of Wyoming regarding their establishment of the Archives of Contemporary History.

4. Presented the Jennings Memorial Lecture at Bowling Green State University

5. Participated in the Symposium on the Quality of Life held at the State University of New York at Oneonta, New York. Title of Paper: $R_x$evolution, Tribalism and the Cheshire Cat.

6. Invited by the American Psychiatric Association to participate in the May 5, 1971 Symposium on Population. My contribution is titled: The Population Crisis Leading to the Compassionate Revolution and Environmental Designing.

Publications:

1. Space and the Strategy of Life, pp 329 to 387 in Behavior and Environment, The Use of Space by Animals and Men, A. H. Esser (Ed), Plenum Press, New York/London 1971

2. Psycho-Ecological Aspects of Population Dynamics, pp 111 to 133 in ENVIRON/MENTAL. Paul Shephard and Daniel McKinley (Eds.) Houghton Mifflin Company, Boston, 1971

3. Transitory Population Optima in the Evolution of Brain. In press in Is There an Optimum Level of Population? S.

Fred Singer (Ed) McGraw - Hill Book Company, 1971.

1. Laboratory of Psychology
2. Section of the Chief
3. Unit for Research on Behavioral Systems
4. Poolesville

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Population, Space and Mental Health

Previous Serial Number: Same

Principal Investigator: John B. Calhoun

Other Investigators: None

Cooperating Units: None

Considerable progress is continuing to be made on this project. However, it has largely been held in abeyance for greater activation for Fiscal Year 1972 after which further report will be made.

Serial No. M-P-C-(C)-39
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Study of heredity and environmental factors in schizophrenia.

Previous Serial Number: Same

Principal Investigator: Paul H. Wender

Other Investigators: David Rosenthal, John Rainer (New York), Laurence Greenhill

Cooperating Units: Research Foundation for Mental Hygiene, Inc., 722 West 168 Street, New York, N. Y. 10032

Man Years:

Total:	3.1
Professional:	2.3
Other:	.8

Project Description:

Objectives: To assess the role of environmental factors in the etiology of schizophrenia.

Methods Employed: The strategy involves the use of adopted subjects to separate the roles of genetic and experimental factors. Since the biological parents are not the parents who rear their children, the transmitters of genetic factors and social experience are separated. In this study we evaluate the psychiatric status and cognitive function of three groups of parents: those who have adopted children who subsequently became schizophrenic; those who reared their own schizophrenic children; and those who reared their own organically impaired offspring.

Psychiatric pathology is assessed by means of structured interviews administered by interviewers who are blind as to the status of the parents interviewed. Cognitive function is assessed by means of a battery of psychological tests.

The design permits a test of three hypotheses: 1 - If psychopathology among the parents of schizophrenics is a cause of the disturbance in the offspring it should be present in both the adopting and biological parents of schizophrenics; 2 - If psychopathology in the parents of schizophrenics is largely a manifestation of a genetically transmitted disorder, it should

be present in the biological and not the adopting parents of schizophrenics; 3 - If psychopathology among the parents of schizophrenics is largely reactive to pathology in the child, it should be present equally in the parents of schizophrenics and of organically impaired children.

The present study, which replicates an earlier study of the adopted parents of schizophrenics, has three methodological improvements: 1 - It employs systematic sampling; 2 - It employs raters who are kept blind as to the status of the parents interviewed; 3 - It employs a comparison group of parents of organically impaired children (controlling for the effect of the child on the parent).

Major Findings: To date 66 cases have been assessed. Evaluation and at least 24 more cases will be completed by June 30, 1971. Data analysis will not be begun until the entire sample has been collected.

Significance to Bio-medical Research and the Program of the Institute: We are attempting to validate our earlier finding which indicated that parental psychopathology did not seem strongly related to the etiology of schizophrenia.

Proposed Course of Project: Data collection will probably be completed by July 1971. Data analysis will require an additional year.

Honors and Awards: None

Publications: None

Serial No. M-P-C-(C)-40
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Changes in neurological and psychological functioning in children with minimal brain dysfunction receiving d-amphetamine.

Previous Serial Number: Same

Principal Investigator: Paul H. Wender

Other Investigators: Monte Buchsbaum, Laurence Greenhill

Cooperating Units: None

Man Years:

Total:	.1
Professional:	.1
Other:	.0

Project Description:

Objectives: To compare neurological and psychological functioning of children with minimal brain dysfunction and normal children and to evaluate the changes produced in the former group following treatment with d-amphetamine.

Methods Employed: The study population consists of a group of normal children and a group of children with minimal brain dysfunction who have manifested a clear-cut clinical improvement following treatment with d-amphetamine.

Both groups will be evaluated to assess positions and changes along the following dimensions: 1 - Average cortical evoked response; 2 - Field dependence.

Children with minimal brain dysfunction are characterized by inattentiveness and stimulus boundedness, both of which appears to change following successful treatment with d-amphetamine. These characteristics (and change in them) may be associated with performance on certain tasks; particularly the Rod and Frame test, and the Petrie task, and in average cortical evoked response to sensory stimuli. It is the purpose of this project to determine if correlates exists between the clinical condition, response to treatment, and test performance.

Major Findings: None. Data analysis is being begun.

Significance to Bio-medical Research and the Program of the Institute: Minimal brain dysfunction is an extremely common syndrome in the pre-adolescent population, occurring in perhaps 5% of that population. Its neurophysiological basis is not understood and its diagnosis cannot be made with accuracy. This project may contribute to an understanding of its etiology and to more accurate diagnostic technique.

Proposed Course of Project: To date 16 children with minimal brain dysfunction and 12 controls have been tested. Data analysis should be completed by December 31, 1971.

Honors and Awards: None

Publications:

Wender, P. H., Epstein, R. S., Kopin, I. J., and Gordon, E. K.: Urinary monoamine metabolites in children with minimal brain dysfunction. Amer. J. Psychiat. In press, 1971.

Serial No. M-P-C-(C)-41
1. Laboratory of Psychology
2. Section of the Chief
3. Unit for Research on Behavioral Systems
4. Poolesville, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Systems Scheme for Behavioral Research

Previous Serial Number: Same

Principal Investigator: Gerald G. Wheeler

Other Investigators: John B. Calhoun

Cooperating Units: None

Man Years

Total:	1.55
Professional	1.05
Others:	0.50

Project Description:

Objectives: To design and develop research methodology, including organizational structure, which has the capacity for such self-appraisal and renewal necessary to promote relevant research in an ever-changing milieu of demands for Science to provide solutions to Health and EnvironMental Health problems.

Methods Employed: (1) Development of means to define structures and processes of environmental settings which determine character and functions appropriate to levels of organization (Systems) persisting within the settings. (2) Development of means to define parameters which permit the Evolution of Systems--the succession of systems through adaptive selection. (3) Design and test, using systems theory and logic, methods for developing and evaluating concepts of research management. (4) Design and test, using systems and information theory and tools, networks of concept communication with other disciplines of relevance such as sociology, architecture-design, and environmental health. (5) Exchange, through conferences, seminars, and consultants, ideas and concepts relevant to these define-design,develop efforts.

Major Findings: (1) An original scheme design in which were

established activity-function sets linked through an organization-management set by information flow axes was altered to make it more adaptable to the organizational environment. The evolved scheme, now being reviewed for implementation, includes objective-goal sets as well as behavior-function sets. The underlying logic in set formulation promotes the development of both an Objective system and a Behavior system lying within the larger (organizational) system. Monitoring and evaluating transactions within and between these two systems should promote more effective management and utilization of resources and ideas. (2) The majority of effort during this report period, however, has been toward and designing and developing a Data Management scheme compatible with both behavior and objectives which will permit mining a very large amount of research data in an efficient and logical manner. This effort has led to structuring information flow from acquisition (of raw behavioral data) through question formulation, analysis, and interpretation to acquisition. Along this information network "user", "monitor" and "programmer" nodes assure appropriate use of person and machine relative to information requirement, dollars, and other resources. Together with a professional data management consultant the staff is structuring for retrieval all research data in a way compatible with objectives, behaviors, and resources.

Significance to Bio-Medical Research and the Program of the Institute: With increased ability to relate its research findings and with increased ability to understand, control, and thus logically alter both its objectives and behavior relative to environmental demands, this organization can more fully contribute to meeting human needs.

Proposed Course of Project: This is a young project. We will continue employing the above methods in the coming year. Sufficient experience, especially with methods now employed internally, should come within the half year and provide documents describing theoretical framework and operational results.

Honors and Awards: None

Publications: none

Serial No. M-P-C-(C)-42
1. Laboratory of Psychology
2. Section of the Chief
3. Unit for Research on Behavioral Systems
4. Poolesville

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Role of Prior Social Experience in Altering Adaptive Behavior

Previous Serial Number: Same

Principal Investigator: Halsey M. Marsden, Ph.D.

Other Investigators: John B. Calhoun, Ph.D.

Cooperating Units: Office of the Director, IR, National Institute of Neurological Diseases and Stroke, NIH. (Principal investigator is on assignment to URBS, CBRY, NIMH from NINDS); Section on Pharmacology, CBRS, NIMH. Dr. Larry Ng, Dr. Robert W. Colburn

Man Years

Total:	0.6
Professional:	0.4
Other:	0.2

Project Description:

Objectives: To determine the influence of prior experience in complex socio-environmental settings on the ability of individuals to reconstitute, functionally, individual behavior and group organization in new settings devoid of the inhibiting, disruptive, or favorable aspects or processes characteristic of the former environment.

Methods Employed: The subjects used to initiate the studies in this project are products of studies included in Project No. M-P-C(C)-37. Data collection, data processing, and techniques of observations adhere closely to methods which have evolved from that Project.

Study 122 - Males undergo social withdrawal in mouse populations at high density in structured habitats. In this study twelve males in each of six groups were introduced to six

new, identically structured, habitats. The groups were as follows:

(1) Aggressors - Dominant, Territorial males.

(2) Pooled withdrawn - Males living in large, all-male groups on the floor of the habitat.

(3) Solitary withdrawn - Isolated, single males living on platforms adjacent to food and water resources.

(4) Beautiful Mice - Males living in small, all-male groups in next boxes. Animals in excellent physical condition.

An old and young sub-category for groups 2 and 4 completed the total of six.

The density in the new habitats was 3 mice/cell in a four-cell habitat, reduced from about 160/cell in the former environment. At a later stage in the study, 72 normal female mice, who had attained prime reproductive age in 6 groups of 12, were introduced to the 6 all-male groups.

Study 123 - In this closely related study, two groups of males (4 in each group) and two groups of females (8 in each group) were selected from a two-celled habitat in which successful reproduction had ceased. For each sex a "beautiful" and a "withdrawn" category was selected. These 4 groups remained in the habitat. The former environment was altered by removing all other animals, a reduction in density from about 160 mice/cell to 12/cell. Following this phase of the study the animals were removed from the habitat and placed in new settings with normal associates of the opposite sex. The 8 males underwent two successive, individual pairings with normal females. The 16 females were placed in a new, identical habitat with an established social group of 8 normal males; and, later, individually paired with normal stud males.

Study 124 - The 4 animals with the highest social velocity (high social status) from each of the 6 groups in Study 122 were reassembled in two new social groups of 12. Conversely the 4 animals with the lowest velocity from each Study 122 group were assembled in two additional groups. Two animals from each Study 122 group having middle social velocity scores comprised a 5th new group of 12. All groups were placed in clean, 4-cell habitats.

Major Findings:

Study 122 - None of the six groups formed a normal social structure. Each group divided into two subgroups: (1) 3 males which exhibited territoriality to varying degrees; (2) 9 which entered, or remained in, states of withdrawal. The territorial males were distributed one to each of 3 cells. All others concentrated in the 4th cell. One animal among the 9 showed a degree of dominance over his fellows, but did not defend territory. Defense of territory was not uniform across groups. It was strongest in the beautiful mice and the aggressors, weakest in the pooled withdrawn, with the solitary withdrawn being intermediate. The level of general social activity followed the same ordering. The pooled withdrawn retained the characteristic pooling behavior, feeding or resting on platforms in aggregates of up to 8 animals.

Reproductive performance of the males with the normal female groups was abnormal and reflected the social structure directly. The 3 or 4 males in each group which had, to varying degrees, recouped the ability to express dominance or territoriality were responsible for 96 of 98 observed copulations. Overall reproductive performance was poor across all groups. Only 15 of the 72 females became pregnant (in a strain where over 95% reproductive success is normally achieved).

Study 123 - Intensive observations over two months revealed no reproductive behavior among the 24 animals. Reproductive failure remained total. In the new settings male reproductive failure continued. None of the two sets of 8 normal, target females became pregnant in individual pairings. Seven of the 16 females did become visibly pregnant while living with the social group of 8 normal males. However, 13 of the 16 females continued to live in the same nest site, (with 32 available in the habitat) and this is where all pups were dropped. The nest was of very poor construction, no more than a sparse mat soaked with urine. Only 5 pups survived to 14 days of age. This was a dramatic example of retention of the "behavioral sink" phenomenon in a new, potentially ideal setting.

When paired in individual nest sites with normal stud males the 16 females produced 50 pups. Upon autopsy female tracts had a total of 73 fresh placental scars. Thus isolation with normal studs produced a marked improvement in reproductive performance; although pathologies remained. All females conceived but 4 did not bring pups to term or immediately cannibalized them. There was evidence of maternal neglect, cannibalism, embryo resorption and possibly spontaneous abortion.

Interestingly 4 spares, (2 males and 2 females) selected and isolated at the time of the reduction of the population from 320 to 24, were individually paired with normal partners. All 4 were successful reproducers. Thus social isolation appears to have a curative effect over time.

Study 124 - The second attempt to socially organize was a failure in all 5 reconstituted groups. There was no evidence of consistent territorial behavior by any animal.

Significance to Bio-medical Research and the Program of the Institute: It is our present conclusion that results of exposure to high-density living, resulting in social withdrawal and maladaptive behavior are largely irreversible in even less complex and ideal environmental settings. Social isolation coupled with time offers some promise of reversibility. If the parallel is made with the human scene, a most pessimistic outlook emerges; for the possible effects of increased urban densities on human mental health will not be alleviated except over generations, even if we act now to reconstruct the social and physical environment. An even more striking sense of urgency should prevail.

Proposed Course of Project: Analysis and interpretation of data is the first priority for the next fiscal year. This must accompany and be closely correlated with the analysis of all data from Project No. M-P-C-(C)-37. This is a massive task but it is only when the individual animal histories are known in an interpretable format that our present insights can be confirmed and new insights gained.

In the slow-decline phase of population history in our 1 remaining crowded population, four groups of 8 animals (4 male and 4 female) will be selected and introduced to new habitats to test reproductive capability. Selection of these animals, to represent 5 behavioral types for each sex, will be biased toward "normality", those kinds of animals most likely to achieve reproductive success.

Continuing collaboration with Drs. Ng and Colburn will give further insight into the nor-adrenalin-adrenalin enzyme system in both adrenal and brain of selected animals.

Honors and Awards: (principal Investigator)

1. Participated as invited discussant, American Psychological Association's Roundtable Discussion of Crowding, Sept. 1970.

Honors and Awards: (Principal Investigator) continued

2. Participated as invited lecturer, University of Pennsylvania's Department of Landscape Architecture and Regional Planning, School of Fine Arts, Feb. 1971

3. Participated as invited lecturer, Catholic University, Washington, D. C., Human Factors Seminar, Department of Psychology, April 1971

4. Participated as invited lecturer, Potomac Chapter, Society for Neuroscience and Neurophysiology Club, Jan. 1971

Publications:

1. Marsden, H. M. Crowding and Animal Behavior. To be published by American Psychological Association in (tentative title) Behavioral Science and the Problems of Our Environment. Editors J. F. Wohwill and D. H. Carson.

Serial No. M-P-C-(C)-43
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Lithium as a therapeutic agent in hyperkinetic behavior disorders of childhood.

Previous Serial Number: None.

Principal Investigator: Paul H. Wender

Other Investigators: Laurence Greenhill, James Weiss, Monte Buchsbaum, Theodore Zahn

Cooperating Units: Office of the Chief, Laboratory of Clinical Science

Man Years:

Total:	1.2
Professional:	1.2
Other:	0

Project Description:

Objectives: To compare the physiological, neurological, and behavioral effects of lithium carbonate and dextroamphetamine sulfate in single blind trials on a hospitalized population of children with the hyperkinetic syndrome who have been unresponsive to amphetamines and phenothiazines.

Methods Employed: Subjects ages 6 to 14 diagnosed as hyperkinetic who have failed to respond to conventional drugs. The subjects are admitted to the NIH. During their first week in the hospital, the children are screened for cardiac and thyroid abnormalities, have routine urinary 17-hydroxy steroid levels taken, and have baseline evoked potentials and autonomic reactivity studies completed. They are placed on a placebo at this time and baseline nurses' behavioral ratings and teachers' ratings at NIH are obtained. During the second week, the children are given dextroamphetamine sulfate (not to exceed 30 mg. O.D., P.O.) and again, 24 hour urines, physiological measures, and teachers' and nurses' behavioral check lists are obtained. During the third and final week, the children are given lithium carbonate (not to exceed 1200 mg. P.O., O.D.), daily lithium blood levels are drawn, and the urines, are obtained. As the child reaches the therapeutic dose level of between 0.8 meq. per liter and 1.2 meq. per liter, he is discharged to home and is followed on a weekly basis in the NIH Outpatient Clinic. Two weeks following the child's first blood level of at least or more than 0.8 meq. per liter, the third set of physiological studies are done on an outpatient basis.

Because of the favorable effects of the small NIH classroom, frequent one to one nursing, and the strict structured environment of the ward, it is difficult to completely evaluate any possible improvement seen in the hospital. The post-hospitalization period is then used as a true single blind study and behavioral check lists are distributed to the child's teacher and the child's own parents. It is one of the major objectives of this project to establish both the safety and efficacy of lithium carbonate treatment in children outside the hospital.

Major Findings: None. To date three children have been treated. It appears that these children handle lithium very well and that safe blood levels can be reached and stably maintained without difficulty. Data on the effectiveness of lithium will not be available until a large sample has been obtained.

Significance to Bio-medical Research and the Program of the Institute: The hyperkinetic syndrome of childhood is an extremely common syndrome in the preadolescent population, but only one-half to two-thirds of these children respond well to current medication. Recent reports by Annell and Dyson have suggested that lithium carbonate may assist some of these formerly unresponsive children. Both reports tend to stress subgroups of the hyperkinetic population, i.e., Dyson has worked with offspring of manic depressives and Annell's success is limited to borderline psychotic adolescence. Furthermore, lithium carbonate treatment may be a less toxic drug than dextroamphetamine sulfate when given over several years' time.

Proposed Course of Project: Data collection should be completed by June 30, 1971. Data analysis should be completed by December 31, 1971.

Honors and Awards: None.

Publications:

Wender, P. H.: Minimal Brain Dysfunction in Children. New York, John Wiley & Sons, Inc., 1971, 235 pp.

Wender, P. H., Epstein, R. S., Kopin, I. J., and Gordon, E. K.: Urinary monoamine metabolites in children with minimal brain dysfunction. Amer. J. Psychiat. In press, 1971.

Serial No. M-P-C-(C) - 44
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS - NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Individual Differences in Eye Movement Search Patterns.

Previous Serial Number: None

Principal Investigator: Monte Buchsbaum

Other Investigators: Adolf Pfefferbaum, Richard Stillman, James Bryan and Lyman B. Wynne

Cooperating Units: Adult Psychiatry Branch
Section on Technical Development, MHIRP

Man Years:
Total: 2.0
Professional: 1.6
Other: .4

Project Description:

Objectives: Development of a computer controlled, interactive, real time eye movement detector; study of individual difference in eye movement with regard to search patterns, information input and feedback; exploration of eye movement characteristics of various psychopathologic groups.

Methods Employed: The apparatus recently developed by this project utilizes a MacWorth eye movement camera stand and a television camera. The corneal reflection of a visible light source is transmitted through an optical system into a television camera. The cartesian coordinates are determined from the video signal by analog devices thus yielding the eye's point of regard at any given time. A process control computer (LINC) is used to generate visual displays and record the analog record data. A data editing system allows calibration of the analogue inputs and conversion of the data to the screen coordinates. The program then outputs the duration and location of each successive eye fixation.

The resultant system provides for the first time an on line process control eye movement recorder and display system. Prior to this development individual difference studies have been prohibitively costly in terms of time required for data analysis. For instance, hand analysis of 10 seconds of eye movements recorded on motion picture film requires four hours to prepare before it could be used as computer input. This stage of data analysis is now completely eliminated and the average subject is run on 20 such 10-second trials.

Experimental Methods: Fifteen normal subjects have been tested on two separate occasions. Each subject viewed a computer display of the outline of two squares; one of which was always the same size and the other a variable size from one presentation to the next. He was given the task of ascertaining whether the variable square was larger or smaller than the standard.

Results: As predicted, there were stable and consistent individual differences. Generally eye movement measures related to duration and number of fixations per unit time (saccadic rate) were the most stable from session to session. Measures related to distance between fixations and total scatter of fixations were less stable. The tendency to begin the task by viewing the standard square first and the time required for the first eye movement were also stable individual characteristics.

Significance to Biomedical Research: Eye movements are important indicators of information input strategies and may therefore reflect psychophysiological styles of information search. The possibility of using this and other objective, physiological measures to better distinguish psychiatric patients is central to psychophysiological research.

Proposed Course of Project: The current system is limited by the tendency of standard vidicon tubes to develop small defects which interfere with the analog triggering circuit. Further, the vidio signal carries a certain noise level which prevents optimal analog detection. A new development, the silicon matrix vidicon tube, has extremely low noise levels and can be defect free with special selection. Only minor circuitry changes are needed to utilize this tube in the present system. Replacement of the standard vidicon tube with the silicon matrix tube has a high priority.

Exploration of genetic factors influencing eye movement and information search has been started. This involves the testing of normal twins and will soon include twin pairs concordant and discordant for schizophrenia. Further methodological studies are also planned.

Honors and Awards: None.

Publications: None.

Serial No. M-P-D-(C)-8
1. Laboratory of Psychology
2. Section on Early Learning and Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Reinforcing Effects of Environmental Stimuli for Infant Behaviors and of Infant Behaviors for Caretaker Actions

Previous Serial Number: Same

Principal Investigator: Jacob L. Gewirtz, Ph.D.

Other Investigators: Barbara C. Etzel, Ph.D., University of Kansas

Cooperating Units: Department of Human Development, University of Kansas

Man Years:

Total:	.25
Professional:	.10
Other:	.15

Project Description:

Objectives: This continuing project has focused on the identification of caretaking patterns that maximize socially-desirable outcomes in children, and that can also make unambivalent the caretaker's relationship to the child. One aim of the experimental phase of the work has been to extinguish undesirable behavior (e.g., high-rate instrumental crying maintained by caretaker attention) in the first weeks of life while fostering (reinforcing) incompatible, socially-desirable responses (e.g., smiling). A second aim has been to determine how, and how early in infancy, diverse social responses can become conditioned or otherwise modified. Another facet of the work has involved analyzing the patterns of attention and care provided children in diverse settings from the view of the effect of those conditions on the actual learning of the child. When the child's learning is different from what caretaker-parents intend, we have termed these cases child-rearing paradoxes. Another aim has been to point up the impact on the caretaker of behaviors of the infant. The caretaker's behaviors can be conditioned at the very same time that the infant's behaviors are being conditioned. A byproduct of these endeavors has been the preparation of manuals on raising and fostering the development of child under both family and group care conditions.

Methods Employed: Children have been observed in a variety of settings, where the behaviors of both the infants and the caretakers have been closely monitored.

Major Findings: As early as the first two months of life, responses like high-rate operant crying, previously reinforced by caretaker attention in a residential nursery, can be decreased experimentally; and smile and eye contact responses could be instrumentally conditioned in that context. The inadvertent maintenance by caregivers of the very behaviors of their charges that they found undesirable is an example of one of the child-rearing paradoxes identified. These paradoxes appear often to result from the use of child-care techniques dictated by theoretical approaches based on unexamined assumptions.

Scientific Significance to the Program of Mental Health Research: Our studies have shown that important aspects of behavior can come under the control of the social environment early in life. This control is observable even when the caretakers do not have insight into the contingencies maintained by the infants' crying. Such demonstrations can be useful in beginning a re-examination of the tactics of caretaking conditions. The provision of attention (love) to babies is insufficient as a prescription for concerned behavior by the caretaking environment. It appears necessary to specify closely the conditions under which the attention is provided, as well as the stimulus components of the attention. For instance, when caretaker attention is not provided with the intention of evoking behaviors from the child, it might best be provided immediately after the occurrence of socially-valued infant behaviors. The demonstrations reported illustrate also how caretaking environments can come readily under the systematic control of consistent behaviors of the relatively young infant.

Proposed Course of the Project: Empirical work has been completed on the first phase of this project. Further focused research studies are planned when our new laboratory facilities become available in 1972.

Honors and Awards: None

Publications:

Gewirtz, J. L. Stimulation, learning, and motivation principles for day-care settings. In E. H. Grotberg (Ed.), Day Care: Resources for Decisions. Washington: Published for the Office of Economic Opportunity by the U.S. Government Printing Office, 1971. Chapter 7, pp. 173-226.

Serial No. M-P-D-(C)-30
1. Laboratory of Psychology
2. Section on Early Learning and Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Stimulus Conditions, Infant Behaviors, Caretaker-Child Interaction, and Social Learning in Diverse Child-Rearing Environments

Previous Serial Number: Same

Principle Investigator: Jacob L. Gewirtz, Ph.D.

Other Investigators: Hava B. Gewirtz, Ph.D., Montgomery College

Cooperating Units: Department of Psychology, Hebrew University of Jerusalem; Computer Science Center at the University of Maryland

Man Years:

Total:	2.20
Professional:	.45
Other:	1.75

Project Description:

Objectives: In this continuing project, diverse behaviors which connote the quality of adaptation and social responsiveness of infants to their environments are being related to stimulus conditions which represent opportunities for adaptive and social learning in early life. Within each of four child-rearing environments, our aims have been: (a) to describe the typical day for the infant, including a catalogue of caretaking schedules, the types of stimuli provided (primarily those provided through interaction with caretakers), and the types and frequencies of behaviors of the infant; (b) to determine the sequential contingencies between environmental stimuli and infant responses insofar as they represent opportunities for learning; and (c) to consider specific performance issues, such as the infant's response to short-term separation from a caretaker to whom he has become "attached" (e.g., his mother), and her responses to his subsequent initiations. It is thought such data can provide a fruitful basis for examining the utility of the concepts available for conceptualizing the child's early experience with his environment.

Methods Employed: Subjects (Ss): Samples of Ss were drawn from the infant population of Israel. One sample consists of 108 Ss in four age groups (8, 16, 24, and 32 weeks) from four child-rearing environments /the Residential Institution, the Kibbutz, the Only-child and the (Youngest-child of) Multiple-child Middle-class Town family/. Each S was observed in his natural setting

Methods Employed (Continued): by a trained woman observer for two half-days, providing data to represent one complete day of his life. A second sample included some 700 infants in the first 18 months of life from the listed environments and a day-care environment as well. Each S was observed once. His smiles, vocal, and other social responses to a woman's face presented in a standard way were recorded.

A codified observation procedure was developed and used. Reliable observation categories and codes were devised for: (a) background events (e.g., mother enters, caretaker talks to visitor, caretaker attends to neighboring child); (b) setting (e.g., feeding, sleeping, bathing); (c) S's behaviors (e.g., smiles, vocalizes, follows, manipulates); (d) the various stimuli provided by (behavior of) the environment, particularly those of caretakers toward S (e.g., mother approaches, caretaker picks up S, father tickles S, caretaker smiles); (e) the sequential contingencies comprising interactions between the infant and his environment; (f) S's gross activity level (e.g., changes position off and on, mouths). Behaviors (but not their durations) were scored as they occurred during the observation period.

Each infant's record, in successive 30-second time units, has been mounted on tape-reels, as have a number of the computer programs required for analyses of event frequencies and rates, and of selected contingencies. Programs for analyzing sequential details of the interaction process have recently been completed. These have been devised to index various aspects of interaction sequences that will serve as dependent variables in group comparisons between Ss, as well as to characterize patterns within a S. Setting and background data have been summarized, as have behavior frequencies and rates and sequences of occurrence of the environmental stimuli provided and of the infants' behaviors. Comparisons within and between the different environmental and age groups are being made via multivariate analyses of variance employing the dependent variables so developed. In this process, after adjusting for time spent by caretakers with their infants, comparisons among environmental groups are being made on: (a) the types and frequencies of stimuli provided infants by caretaker-adults (through gross physical contact like lifting, fine physical contact like tickling or nuzzling, as well as talking, smiling); (b) the types and frequencies of infant responses to or in the presence of the adults (e.g., looking, smiling, vocalizing, crying, motor responding); and (c) the incidence and details of patterns of interaction between caretaker-adults and the infant.

Major Findings: Analyses recently performed have dealt with caretaker and child behavior counts for the entire observation day, ignoring their concurrent and sequential contingencies. The findings indicate difference patterns, by environmental group and by infant age, in caretaker behaviors as well as in infant responses. For three caretaker behaviors categories exhibited to children, Gross contact, Fine contact, and Smiles, the child-rearing group means rank-ordered (from highest to lowest): Only-child, Kibbutz, Youngest-child, Institution. (The only exception to this pattern was Talking, where the Youngest-child group mean was higher than the Kibbutz mean.) These

Major Findings (Continued): results indicate that the behaviors of the Kibbutz child's mother and caretaker together provide him with stimulus provisions rather like the pattern provided infants by mothers in nuclear-family homes and, indeed, in that frame often more like that provided to Only- than to Youngest-children. In that context, the mean numbers of Adult Talk and Smile responses tended to increase with child age, while those of Gross Contact and Fine Contact remained constant.

The pattern of behaviors exhibited by caretakers to children was also found to depend on setting--that is, whether the adult was providing care to her infant (feeding, bathing, diapering, or dressing him) (we have termed this "caretaking time") or whether she was simply present but not providing care (we have termed this "pure-social time"). Caretaking time comprised but a small fraction of the time adults were in the vicinity of their charges. In the Only- and Youngest-child nuclear family home settings, on the average more of each of the four classes of adult behaviors were provided to the children during Pure-social than during Caretaking time. This difference was less pronounced in the Kibbutz setting and reversed in the Institution setting. Thus, Institution infants received most of their stimulation from caretakers during the rather small portion of the day when they received bodily care.

With the exception of Watching (looking), a basically similar mean result pattern was found for each of the five discrete infant behavior classes observed in the presence of caretakers: most responses were made by the Only-child group, least by the Institution group, with the Kibbutz and Youngest-child groups intermediate. However, for Watching responses the mean pattern changes according to the age of the children.

The mean patterns of child behavior exhibited in the presence of caretakers in Pure-social and Caretaking settings were also similar to those for the adult behaviors in those settings. Only- and Youngest-child group means were higher during Pure-social than during Caretaking time, while the similar Kibbutz pattern was less marked between the two settings. Again, there were more child behaviors exhibited in the Institution during Caretaking than during Pure-social settings.

It is difficult to assign the label "cause" and "effect" differentially to the adult and child behaviors. It seems prudent in an "in vitro" analysis that sums behavior over the entire day separately for the infant and for his caretaker to report only the very similar patterns of adult and child behaviors examined in terms of age and environmental group membership as well as of Pure-social vs. Caretaking setting. In subsequent analyses, we shall be examining the contingent relations within interaction sequences that occurred between child and adult behaviors.

Further, outside of caretaking occasions, mothers exhibited more fine contact responses (e.g., tickling, nuzzling) to their sons than did fathers. Specifically, as the age of the infant increased, kibbutz mothers showed increasingly more fine physical contact with them, multiple-child mothers

Major Findings (Continued): decreased their physical contact, and single-child mothers remained constant in this behavior. However, this order was reversed for the fine contact exhibited by fathers to their sons. Mothers also smiled more, talked more, and exhibited more physical gross contact to their sons than did fathers. Further, kibbutz mothers smiled more and kibbutz fathers smiled less to their sons at 6 and 8 months of age than did town-family parents. Comparable differences are being identified on other child and caretaker responses in a variety of environmental contexts.

Scientific Significance to the Program of Mental Health Research: Smiling, vocal, and similar adaptive behaviors constitute key response systems in the human, for they mediate (and hence can also index) much of initial adaptive and social learning and development of the infant, as well as his subsequent patterns of social-interaction. A developmental map of the early course of these behavior systems can be of considerable use in itself, but can also provide a context for understanding the nature of the outcomes of different conditions of child-rearing. These conditions can be assumed to provide differential varieties and amounts of stimulation, and hence varying opportunities for social learning.

Proposed Course of the Project: Analyses of the data are continuing. Reports for publication are being issued at regular intervals, as they are completed.

Honors and Awards: None

Publications: None

Serial No. M-P-D-(C)-34
1. Laboratory of Psychology
2. Section on Early Learning and Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Deprivation and Satiation of Social Stimuli as Determinants of their Reinforcing Efficacy

Previous Serial Number: Same

Principle Investigator: Jacob L. Gewirtz, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.40
Professional:	.10
Other:	.30

Project Description:

Objectives: There are potentially a great variety of contextual conditions which, on any particular occasion, could determine the power of a focal stimulus in evoking, cueing, or reinforcing behavior. These conditions, whose effects often cumulate, may operate concurrent with focal stimulus functioning, or in a period or at points preceding the point of focal stimulus presentation. Our aim has been to survey the range of such contextual factors that can qualify stimulus efficacy, to make a preliminary categorization of them, and to consider some underlying issues in their operation.

Methods Employed: The empirical portion of this program has been aimed at manipulating some key contextual factors, in particular implementing satiation and (the reciprocal) deprivation conditions for a social stimulus class. This was effected by varying the availability of a social stimulus to subjects in a period immediately preceding a test for its effectiveness. A secondary aim has been to implement different maintenance patterns of prior stimulus availability.

Major Findings: Data from diverse sources were surveyed to identify classes of contextual factors. In this frame and on the basis of the empirical studies earlier conducted, we were led to the conclusion that the function of a stimulus on a particular occasion, in evoking, cueing, or reinforcing behavior, may be enhanced or decreased by the manipulation of the context of stimulus provision. Indeed, even the direction of the effects of a stimulus on behavior may be determined by the stimulus context. That is, whether the same stimulus

Major Findings (Continued): evokes approach or avoidance responses will often depend entirely on the context of its provision.

Scientific Significance to the Program of Mental Health Research: As the efficiency of human learning and performance depends on the effectiveness of the available stimuli in each of their roles, the identities of contextual setting conditions can provide an important key for understanding the acquisition and performance of child behavior systems, particularly in natural settings. The principles identified should also bear on such conceptions as childhood "privation," as they suggest that effective stimulation depends not only on the type and number of stimuli available but also on the contexts of their provision as well.

Proposed Course of the Project: Our plan is to mount further experimental studies under this continuing project when new laboratory facilities become available in 1972.

Honors and Awards: None

Publications:

Gewirtz, J. L. Some contextual determinants of stimulus potency. Monographs of the Society for Research in Child Development, in press.

Serial No. M-P-D-(C)-42
1. Laboratory of Psychology
2. Section on Early Learning and Development
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Evaluation of Concepts Employed in Analyses of Early Learning and Development

Previous Serial Number: None

Principle Investigator: Jacob L. Gewirtz, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	1.15
Professional:	.35
Other:	.80

Project Description:

Objectives: To analyze the role in theory and research of focal concepts employed in the area of early adaptive and social learning and behavioral development, and thereby to provide a basis for evaluating and facilitating researches in those sectors. Included are such concepts as development, critical period, environmental stimulation, drives and motivation, stimulus privation, privation-deprivation and separation, attachment and dependence, imitation and identification, vicarious-reinforcement and observational learning.

Methods Employed: While the moment-to-moment details of the interchange between stimuli and responses are relevant to nearly every process theory of learning and development, researches done under the aegis of such theories have almost routinely employed global concepts for environment and behavior (e.g., traits) that only summarize through lengthy time spans the occurrence of either stimuli or responses but not both facets of the S-R interchange. These research variables are therefore remote from the level of analysis required by the process theories that have spawned them. Rather than emphasize such summarizing concepts, our approach to human social learning has proceeded as a detailed functional analysis of stimuli and responses, their interchange at a particular moment (i.e., the stimulus-response unit), and the sequences of interaction across successive moments (i.e., the stimulus-response chain). The conditioning concepts we have employed thus order environmental operations

Methods Employed (Continued): that effect systematic and reversible changes in observable behaviors. The approach employed is open to the addition of new concepts as required, and to the differentiation and refinement of the concepts in current use.

Major Findings: Progress was made during the year in evaluating the adequacy of several key concepts in ordering the behavioral phenomena for which they have been devised, and in relating them to our observations in child-rearing settings: (1) Under a conditional-discrimination learning paradigm, we have advanced an analysis for the acquisition of a functional imitative response class. It is assumed that this class, containing a potentially unlimited number of instrumental responses matched to diverse reinforced and nonreinforced responses of models (or one model), can be acquired through the routine intermittent, extrinsic reinforcement of some members of that class. This conception can account for the pervasiveness of imitation, its focus on one model, its occurrence when the model is absent or when there is no extrinsic reinforcement for imitation, and the acquisition of behaviors that can be topographically quite different from the model's. A functional learning approach, therefore, can account for the very phenomena that have prompted others to postulate seemingly unparsimonious and nonempirical principles such as the operation of intrinsic reinforcement or cognitive processes as well as of observational learning and vicarious reinforcement. Further, without the use of motivational constructs, the imitative-learning paradigm seems parsimoniously to account for the phenomena usually grouped under the identification process, by which the child is said to acquire the motives, ideas, and values of another person (or others). (2) We have considered some theoretical and empirical issues critical to "vicarious-" and "self-reinforcement" phenomena. Although such behaviors at first may appear to be anomalous under the instrumental-conditioning paradigm and the Empirical Law of Effect, our analysis indicates that such phenomena may be accounted for plausibly in terms of operational-conditioning conceptions in which extrinsic reinforcement plays a key role. A unique conception of "self-" or "intrinsic-reinforcement" to explain response occurrence in the seeming absence of extrinsic reinforcement, and the use of inexplicit cognitive terms like "self-evaluation" as central to that process, would therefore be entirely unnecessary in a straightforward learning analysis. As a conceptual framework for evaluating the vicarious-reinforcement effects, the more general phenomenon of observational learning was considered. There are theorists who assume that learning-by-observation is a primary, prepotent acquisition process, a capacity of the organism as it were. However, it seems that researchers have rarely attempted to rule out the possibility that such phenomena may represent a case of routine instrumental conditioning where the presence of a demonstrator-model only functions to expedite the conditioning procedure. Furthermore, none of the many researchers on what is taken to be learning-by-observation has yet implemented the necessary controls (or assessments) for possibly relevant experience, to rule out either the possibility that an organism may learn to learn-by-observation or the possibility that stimuli provided under an experimental condition may earlier have been conditioned to control the relevant response. (3) Dependence and attachment have been evaluated critically and models advanced for their acquisition and maintenance. These terms were thought best conceptualized as abstractions for classes of functional

Major Findings (Continued): relationships involving the positive stimulus control over a wide variety of an individual's responses by stimuli provided either by a class of persons (dependence) or by a particular person (attachment). In this context, conceptual analyses are being prepared on: the origins of attachment and dependence, and distinctions between the concepts; as well as the assumptions underlying cognitive-ethological and learning approaches to human attachment and the mother-infant relationship. When the phenomena classified under the terms attachment and dependence are not conceptualized in a functional way, the distinction between the terms and their fundamental characteristics (that can account for the apparent intensity sometimes said to underlie attachment behaviors) may be obscured. As dependence and attachment are gross abstractions, many types of behaviors (approach, preference, approach in the context of avoidance, and disorganization behaviors) could be used to index each of them. Considerations are being outlined for the selection of indices under different research strategies and tactics.

Scientific Significance to the Program of Mental Health Research: Clarification of the purpose and utility of concepts like imitation and identification, vicarious reinforcement, and observational learning, and attachment and dependence should lead generally to more efficient mental health research and application. Also, the role of response acquisition in various complex personality processes and distinctions between motivation and learning concepts can be made more explicitly and more parsimoniously. On this basis, research and engineering applications in the area of psychological development should be facilitated.

Proposed Course of the Project: It is thought that the need for this project is a continuing one, as concepts like the ones being analyzed are in common use in the field at large.

Honors and Awards: None

Publications:

Gewirtz, J. L. The ubiquitous role of extrinsic reinforcement in "self-" and "vicarious-reinforcement" phenomena and in "observational learning" and imitation. In R. Glaser (Ed.), The Nature of Reinforcement. Columbus, Ohio: Charles E. Merrill Books, Inc., 1971. Pp. 279-309.

Gewirtz, J. L. Conditional responding as a paradigm for observational, imitative learning and vicarious-reinforcement. In H. W. Reese (Ed.), Advances in Child Development and Behavior. Vol. 6. New York: Academic Press, 1971, in press.

Serial No. M-P-P-(C)-6
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Investigation of Some Formal Characteristics of Speech

Previous Serial Number: Same

Principal Investigator: Donald S. Boomer, Ph.D.

Other Investigators: Allen T. Dittmann, Ph.D.

Cooperating Units: None

Man Years

Total:	2.04
Professional:	.80
Other:	1.24

Project Description:

Objectives:

General: To elaborate and test a psycholinguistic theory of speech performance.

Specific: To explore the psychological properties of some functional speech units specified by the theory.

Methods Employed:

1. Linguistic and phonetic analysis of natural speech utterances.

2. Controlled experimental situations which systematically vary parameters of speech production and perception, and their correlates.

Major Findings:

An extended research program, summarized in previous annual reports has been incorporated into a developing theory of speech production. In bare outline, the theory posits a central speech planning mechanism which assembles motor production programs which, in turn, control the external articulators during actual speech production. The pre-planning aspect of this theory distinguishes it from more conventional associative theories

which explain speech production in terms of associative bonds between elements: i.e., words and/or sounds.

Major findings from this project, previously reported, include demonstrations that speech non-fluencies such as hesitations, repetitions, and tongue-slips are not random "noise" but occur lawfully with respect to the functional speech units posited in the theory. During the past year some relationships between respiration and speech were studied. The object of this investigation was to determine how speech rhythms and the respiratory cycle are mutually accommodated in normal speech. One methodological study examined the procedure whereby another investigator (Goldman-Eisler) had found fear and anxiety to be associated with lower-than-normal rates of breathing while speaking. A carefully controlled replication demonstrated a methodological artifact in the previous study which invalidated its conclusions.

In a study of speech-breathing interaction the breathing component was manipulated by the introduction of mild expercise to increase respiratory frequency. While it was found that inspirations occurred predominately between phonemic clauses and only rarely at within-clause hesitations, individual differences proved to be far larger than originally expected. Inspirations at hesitation pauses (as compared with inspirations at juncture pauses) ranged from 7% for one subject to 41% for another, with an average at 24%. Such wide individual differences make it impossible to infer universal tendencies for the interlacing of speech rhythm and breathing. That they are interlaced is beyond question (and beyond chance for all subjects), but the relationship between speech rhythm and a number of other variables which have been studied in this research program is far closer than this one.

From data analyzed to date there appears to be a slight increase in frequency of inspirations at hesitation pauses compared with juncture pauses after exercise, an increase which was not statistically significant. The increase in respiration rate with this amount of exercise was, however, a significant one. Thus the demands of the speech system appear to remain dominant under this amount of stress. An interesting side finding is that some subjects do not apparently increase their rate of breathing to compensate for this exercise, but rather breathe more deeply. Thus not all subjects tested thus far have been suitable for this type of analysis, and the project could not be completed on schedule.

Scientific Significance to Mental Health Research Program:

Behavioral and medical research involving speech function, studies of psychotherapy and aphasia, for example, are hampered by the lack of appropriate psychological theories of speech production. Most current linguistic theories are inappropriate in that they aim to describe abstract language structures without reference to the live users of the language, thus failing to link with theories and data in psychology and neurophysiology. The

theory underlying the present program is broadly psycholinguistic in scope and can thus accommodate data and observations from other relevant disciplines. Of more direct benefit to the field of neurophysiology is the fact that this work provides a detailed, structured analysis of the output of an important motoric system. Such analysis will be necessary as neurophysiology increasingly attempts to deal with the complex sequential behavior.

Proposed Course of Project:

A number of lines of investigation will be pursued in the coming year.

1. A continued attempt to separate the processes of word-finding and syntactic framing -- the so-called paradigmatic-syntagmatic distinction proposed by Jakobson.

2. Continued exploratory studies of the relationship between short-term memory load and fluctuations of pupillary diameter. The phonemic clause theory of speech posits that incoming speech be stored or "buffered" until the end of a phonemic clause at which time the whole clause is decoded as a pattern of sound and sense. In another situation (Kahneman and Beatty, 1966, Science, 1954, 1583-1585) pupillary diameter has been demonstrated to increase as incoming information was stored. It is hypothesized that fluctuations in pupillary diameter in subjects listening to speech will be found to index the major unit boundaries posited by the theory. During the past year a replication of the Kahneman and Beatty work has been carried out with findings which generally support their conclusions. A set of speech stimuli are being prepared in order to test the hypothesized buffering process of speech perception. This test will be undertaken during the coming year.

3. The study of speech and respiration will be continued. Subjects in a second study will be exercised more strenuously in an attempt to eliminate some of the variance due to individual differences.

Honors and Awards: None

Publications:

Boomer, D. S.: Review of Psycholinguistics: Experiments in spontaneous speech, by Frieda Goldman Eisler. Lingua. 25: 152-164, 1970.

Goodrich, D. W. and Boomer, D. S.: Experimental assessment of modes of conflict resolution. Family Process, 2: 15-24, 1963. Reprinted in N. W. Ackerman (Ed.): Family Process Reader. New York, Basic Books, 1970, 431 pp.

Boomer, D. S.: Review of Rhythms of Speech by Jaffe and Feldstein. Contemporary Psychology. In press.

Serial No. M-P-P-(C)-22
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Development of Potentially Creative Scientists: Personality Characteristics Associated with Creative Performances

Previous Serial Number: Same

Principal Investigator: Morris B. Parloff, Ph.D.

Other Investigators: Kenneth Burgdorf, Ph.D.

Cooperating Units: None

Man Years

Total:	.66
Professional:	.40
Other:	.26

Project Description:

Objectives:

To conduct a longitudinal study to assess the nature, degree and correlates of personality change evidenced by highly selected samples of male subjects judged to be highly creative, as well as those judged to be less creative. This aspect of the study covers a five year period following high-school graduation.

Methods Employed:

In accordance with the plans for this longitudinal study, a battery of tests was readministered in 1970-1971 to a sample of approximately 400 subjects (Beta Sample) who had been previously identified and tested in 1965 and 1966. The Personality, Social Adjustment and Performance measures employed are identical to those administered to another sample of approximately 500 students (Alpha Sample) who had been studied by these investigators in 1963, 1964 and 1969. The Battery included the California Psychological Inventory, four scales from the MMPI, a specially devised Social History Questionnaire, Parent-Child Relationships Inventory and other instruments related to achievement, recognition, and creativity.

Major Findings:

The materials obtained from the most recent survey of the Beta sample have not been completely analyzed.

Scientific Significance to Mental Health Research Programs:

Factors which influence personality development and motivation are known to facilitate or impede the full use of ones capacities. While this issue is of significance in affecting the development of all individuals, it is of particular importance in aiding us to understand the impact of social and cultural influences on uniquely gifted individuals who demonstrated "creative" abilities at an early age.

Proposed Course of Project:

Data analyses will be completed with particular emphasis on relating personality change to both early antecedents and recent experiences of these subjects.

Honors and Awards: None

Publications:

Parloff, M. B.: Creativity research program: A review. In Taylor, C. W. (Ed.): Climate for Creativity. Elmsford, New York, Pergamon Press. In press.

Serial No. M-P-P-(C)-30
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Parent-Child Relationships Perceived by More and Less Creative Adolescents and their Parents

Previous Serial Number: Same

Principal Investigator: Morris B. Parloff, Ph.D.

Other Investigators: None

Cooperating Units: None

DISCONTINUED

Serial No. M-P-P-(C)-40
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Body Movement as Expression of Change in Psychological Tension States

Previous Serial Number: Same

Principal Investigator: Allen T. Dittmann, Ph.D.

Other Investigators: Donald S. Boomer, Ph.D.

Cooperating Units: None

Man Years

Total:	.74
Professional:	.50
Other:	.24

Project Description:

Objectives:

To continue to explore body movements as emotional responses. In the past, movement frequencies have been the focus, but now form of movements will be added, using video tape recording to get at these variables. The reason for the change is that results from other laboratories in this general area, chiefly from Freedman at the Downstate Medical Center and Ekman from Langley Porter Clinic have shown that discrete, rhythmical movements and continuous movement may be separated with high reliability by examining records of behavior sequences on video tape.

Methods Employed:

Equipment has been selected, and some has been put into operation. In the first experience with it, we have learned a good deal about its repeated compromises between the demands of precision of measurement and representative sampling of material.

Major Findings:

None at this phase.

Scientific Significance to Mental Health Research Program:

There are two sorts of contributions which this area of work can make: 1) the more immediate one of specifying how people express themselves under different circumstances so that clinicians may be taught to "read" their patients more accurately and consequently serve them more effectively; and 2) the longer term one of enabling us to gain a foothold on social interaction, specifically on the details of conversation regulation so that the effects of a number of families of variables (social structural, individual personality, and so on) on this system can be studied.

Proposed Course of Project:

To develop the means of collecting the data necessary to carry this work forward.

Honors and Awards: None

Publications: None

Serial No. M-P-P-(C)-41
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Survey of Literature on Emotional Communication

Previous Serial Number: Same

Principal Investigator: Allen T. Dittmann, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.74
Professional:	.50
Other:	.24

Project Description:

Objectives:

1. Completion of a volume on conceptual organization of emotional communication and its application to research methodology in studies of emotional communication.

2. To test the application of another aspect of communication theory to the research situation. In this case the study was prompted by the publication of Kinesics and Context by Ray L. Birdwhistell and an invitation from the journal Psychiatry for a review of it. Kinesics is a discipline proposed by Birdwhistell in which body movements and facial expressions are to be studied by methods parallel to those of linguistics. The underlying assumptions are that basic movement events are similar to speech events and they are arranged by some internal organization similar to that of syntax and grammar of language. The first of these assumptions may be examined in the light of the communication theory classification of information sources as either discrete or continuous: basic speech events are discrete, and we may look for evidence that basic movement events are discrete as well.

Methods Employed:

1. Standard library research methods, aided by attendance at conferences and by correspondence and visits with the major workers in the field.

2. This study reviewed all measures of movements and other expressions used here and by other investigators to determine how many of the underlying variables could be construed as discrete. For the purposes of this study, discrete meant that the way the events occur, their variations could be described by a set of non-overlapping categories.

Major Findings:

1. The monograph, Interpersonal Messages of Emotion, was submitted for publication.

2. The study of types of information sources shows that there are a few movements and expressions which are properly conceptualized as discrete variables, but that there are far more which are not. Examples of the former are head nods, studied in previous years in Project M-P-P-(C)-40, certain facial behaviors studied by Tomkins and Ekman, a few postural events such as the arms akimbo position studied by Mehrabian, and certain phenomena of gaze direction studied by Kendon. The majority of movement and postural phenomena, however, are plainly continuous in nature: the body focused movements of Freedman & Hoffman (almost self-caressing movements), degree of body lean toward or away from the conversational partner, distance between partners, and the like, are examples. Even those movements which are performed discretely in time, like the rhythmical speech-accompanying movements, are for the most part not classifiable into discrete categories, but are more tied to speech rhythms. From the research which has been done so far, it appears that there are not enough discrete movements to make up a very rich "body language" parallel to speech. This is not to say that body movements and facial expressions are not communicative in day-to-day social interaction, but that the methods developed for linguistics are not appropriate to the study of these movement events.

Scientific Significance to Mental Health Research Program:

Although the original focus of this work was to develop measures for process research in psychotherapy, its significance has broadened so that it will have wider use in designing experiments in social perception generally and the diagnostic process specifically.

Proposed Course of Project:

The results of the sequential probability studies of previous years in this project will be put to use in the apparatus of Project M-P-P-(C)-40 as described before. The results of the present study of information sources will be formalized into a set of criteria for determining the discrete-

continuous nature of the variables which that other project begins to develop with the new video techniques now available to it.

Honors and Awards: None

Publications:

Dittmann, A. T.: The body and movement-speech rhythm relationship as a cue to speech encoding. In Siegman, A. W. and Pope, B. (Eds.): Studies in Dyadic Communication. Elmsford, New York: Pergamon Press. In press.

Dittmann, A. T.: Review of "Kinesics and Context" by Ray L. Birdwhistell. Psychiatry. In press.

Serial No. M-P-P-(C)-42
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychotherapy Research: Models and Conceptions

Previous Serial Number: Same

Principal Investigator: Morris B. Parloff, Ph.D.

Other Investigators: Allen T. Dittmann, Ph.D.; Donald S. Boomer, Ph.D.; Kenneth Burgdorf, Ph.D.

Cooperating Units: None

Man Years

Total:	1.45
Professional:	.60
Other:	.85

Project Description:

Objectives:

A. General: To develop basic methodology in psychotherapy research which will enhance the systematic accumulation of knowledge prerequisite to answering the basic question: "What therapists, using what kinds of techniques, under what kinds of conditions, with what sorts of people, produce what kinds of effects?"

B. Specific:

1. Help seeking behaviors of talented science students:

a. To examine the incidence and nature of (psychiatric) help seeking behavior in a sample of unusually talented science students.

b. To examine the antecedents of help seeking behavior.

2. Mechanisms of change and instrument development:

a. Outcome measures

b. Encounter group techniques.

Methods Employed:

1. Help Seeking Study

A sample of 535 exceptionally talented science students was identified in 1963 during their senior year of high school. In 1965, a replication sample of 402 similar students was identified. A wide variety of information--including indices of personality traits, parent-child relationships, interests, activities, achievements, etc.--was collected on each sample at several points in time beginning at the time of identification and concluding five years later (late summer of 1970 for the replication sample). The most recently administered questionnaire contained several items dealing with help seeking behavior during college. These items were used to divide each sample into four groups: (1) students who report that they have never seriously considered seeking help for psychiatric problems; (2) students who report having considered seeking but not actually seeking help; (3) students who report having sought help, but having left therapy after five or less sessions; and (4) students who report remaining in therapy for more than five sessions. Groups (1) and (4) were compared on a variety of measures, and the characteristics of groups (2) and (3) were also examined, although less extensively.

2. Mechanisms and Instruments

Following intensive reviews of the "outcome" literature, a series of conferences were held under the sponsorship of the Clinical Research Branch, NIMH. The aim of these meetings has been to propose a coherent and consistent set of outcome measures for use in studies of psychotherapy induced change. An instrument permitting systematic review of reports of psychotherapy studies and the reliable assessment of the adequacy of such studies was devised by members of this section.

Major Findings:

1. Help Seeking Study

It was found that 56% of the 756 students reported that they had "never considered" entering psychotherapy. The 44% who had considered psychotherapy included 20.5% who had never sought help and 23.5% who had sought treatment. Of those who entered treatment only 12.5% (95 subjects) remained in treatment longer than five sessions.

In reviewing the reasons given by the group that "had considered but never entered psychotherapy," it was found that the chief reasons were lack of confidence in psychotherapy and the judgment that their problems were "not severe enough to warrant treatment." Additional reasons, such as "lack of awareness of psychiatric facilities," "lack of money," and "fear of stigma" were only rarely given.

Of particular interest is the finding that the personality measures obtained while the students were yet in high school were strongly associated with subsequent help seeking behavior. The predictive efficiency of 10 personality measures were found to be stable on a replication sample.

It was further found that personality data could be used to differentiate between those subjects who had never considered psychotherapy and all others, i.e., had merely considered or had actually entered some form of treatment. One can also predict, but with less efficiency, how long a subject who enters therapy will remain in treatment. The data obtained thus far, however, permit discrimination between those who consider seeking help but do not enter therapy and those who consider and actually do enter therapy. It appears, therefore, that the most critical step in the help seeking process -- that of making a decision to enter treatment -- is, paradoxically, the least predictable. This finding suggests that the decision to seek or not to seek help may be critically influenced by events in the immediate environment (e.g., attitudes of peers, group mores, experience of friends who entered psychotherapy, etc).

2. Mechanisms and Instruments

A conference report listing recommendations for a battery of outcome measures is in preparation. The psychotherapy review instrument is currently being applied to the survey of group psychotherapy literature. The findings are incomplete.

Scientific Significance to Mental Health Research Program:

1. Help Seeking

This study gives further evidence that mental health programs concerned with identifying community psychiatric needs and "manpower" needs must be concerned with the critical fact that "patienthood" is defined by the patient rather than by the mental health practitioner. Mental health needs will vary markedly with the changing attitudes and explanations of society toward "mental illness," "psychiatry" and "well-being." At present the personality characteristics of those who feel the need of psychotherapy and seek it and those who feel the need and decide not to seek help are indistinguishable.

2. Mechanisms and Instruments

The basic question in the area of psychotherapy is complex and cannot be answered by unsystematic studies unless the varieties are consistently identified and measured in standardized fashion in all studies. A cumulative body of knowledge cannot be achieved unless the basic tools are devised and employed widely.

Proposed Course of the Project:

1. Help Seeking Study

Data analyses will be completed and reports will be prepared for publication.

2. Mechanisms and Instruments

The effort to identify mechanisms and techniques for enhancing psychotherapy has involved a continuing study of a variety of encounter groups. Pilot work in utilizing some procedures borrowed from encounter groups, T-groups, and Gestalt therapy have been undertaken to enhance two important conditions of treatment: 1. Group cohesiveness; 2. The frequency and intensity of the affective experiences of the participants.

In cooperation with Dr. Martin Katz and his staff, research plans for assessing the effects of specific encounter techniques with specified participants are being developed.

Honors and Awards: None

Publications:

Fiske, D. W., Hunt, H. F., Luborsky, L., Orne, M. T., Parloff, M. B., Reiser, M. F., and Tuma, A. H.: Planning of research on effectiveness of psychotherapy. Arch. Gen. Psychiat. 22: 22-32, 1970. Reprinted in Amer. Psychol. 25: 727-737, 1970.

Yalom, I. D., Fidler, J. W., Frank, J., Mann, J., Sata, L., Parloff, M. B., and Seashore, C.: Encounter groups and psychiatry. Report of the American Psychiatric Association Task Force on Recent Developments in the Use of Small Groups. APA Task Force Report #1, April 1970, 27 pp.

Parloff, M. B.: Group therapy and the small group field: An encounter. Int. J. Group Psychother. 20: 267-304, 1970.

Parloff, M. B.: Sensitivity groups: Sheltered workshops for the alienated, a discussion of Carl Goldberg's article "Group sensitivity training experience." Int. J. Psychiat. 9: 197-204, 1970-71.

Parloff, M. B.: Review of "The Theory and Practice of Group Psychotherapy," by Irvin D. Yalom. Int. J. Group Psychother. 31: 109-110, 1971.

Serial No. M-P-P-(C)-43
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Measures of Creative Ability in Science

Previous Serial Number: None

Principal Investigator: Morris B. Parloff, Ph.D.

Other Investigators: Kenneth Burgdorf, Ph.D.

Cooperating Units: None

Man Years

Total:	2.45
Professional:	1.20
Other:	1.25

Project Description:

Objectives:

1. To examine the interrelations among eight measures of scientific creative ability.

2. To assess each measure's "definition" of creative ability, by examining its relationships with a wide variety of variables: measures of interests, activities, aptitudes, achievements, self-perceptions, personality traits, etc.

3. To examine the extent to which each measure of "scientific creative ability" (obtained on a sample of high school seniors) is predictive of subsequent activity and achievement in science (as assessed by measures obtained five years after high school graduation.)

4. To assess the relative advantages and disadvantages of the approaches to measurement represented in the study.

Methods Employed:

1. The design of the study was longitudinal, extensive questionnaire data being collected at each of three points in time: 1965 (when the subjects were high school seniors), 1966 (after the subjects' first year of college), and 1970 (after many subjects had completed their first year of graduate school).

2. The initial sample was composed of 402 subjects. College data were collected from 351 subjects (87%), post-college data from 307 subjects (76%).

3. Each of the subjects submitted a report of a scientific research project which he had conducted while in high school and a report of his activities, achievements, and awards in science. These data were used to form two measures of creative ability: a product measure, derived from expert evaluations of the creativity of the research project, and a recognition measure, derived from the report of achievements and awards. Six additional measures were derived from published paper-and-pencil tests administered to a sub-sample of 131 subjects.

4. Chi square and t-tests were used to relate the creative ability measures to one another and to measures obtained from the various questionnaires. These analyses have been completed for the high school and college data. The post-college data are currently in the final stages of preparation for analysis.

Major Findings:

1. The findings to date have been uniformly negative for the "Test" measures of creative ability. None of the test measures was related in the expected manner to any other measure of creative ability (including self-ratings of creativity) and none of them was related to any of the measures of scientific activity or achievement. Each of the tests was generally unrelated to measures of personality traits, and to measures of activity and achievement in extracurricular areas other than science. Contrary to expectation, several tests were found positively associated with measures of academic aptitude and academic achievement.

2. Although positively related to one another, the "Product" and "Recognition" measures produced quite different patterns of correlates. Recognition was independent of measures of academic aptitude-achievement and of family background (e.g., socio-economic status) but strongly related to measures of activity and achievement in extraacademic fields other than science. The reverse was found for the Product measure. Both were positively associated with measures of scientific activity and achievement, creativity self-ratings, and personality traits often discussed as related to creativity, although the strength of association was consistently greater for the Recognition than for the Product measure.

3. Assuming the post-college data will be consistent with the data already analyzed, several tentative conclusions may be made: (a) The three types of measures of creative ability investigated--Test, Product, and Recognition--differ substantially, one from another, in the way they "define" the construct. The Recognition (i.e., achievement) measure behaved most in accord with theory-generated expectation, the Test measures least in accord with expectation. (b) Research conclusions regarding the nature of creative ability in science may be expected to be affected strongly by the particular manner in which the construct is measured. (c) It may prove more useful in the long run to develop measures of creative ability by utilizing a criterion-centered, empirical model (as used in the development of instruments such as the Stanford-Binet and the MMPI) rather than the currently fashionable hypothetico-deductive model.

Scientific Significance to Mental Health Research Programs:

An absence of definitional consensus at the abstract, theoretical level is a problem not unique to the creativity literature. Theoretical controversy has always been a major aspect of the literature on intelligence, for example. An interesting feature of the intelligence literature is that, in spite of theoretical controversy, a remarkable degree of consensus has been attained at the level of operational definition. It is rare to find a test of intelligence which is not at least moderately related to other intelligence tests and to measures of academic aptitude-achievement. Probably the most significant contribution of this study is that it demonstrates the extent to which the creativity literature does not enjoy a similar operational consensus. The results suggest the advisability of a reordering of research priorities, away from substantive questions and toward methodological ones. Until some degree of agreement is attained regarding the measurement of creativity, it will be impossible for the field to generate an internally consistent body of substantive research findings. As noted above, the results also suggest a potentially fruitful approach to the development of measures of creative ability.

Proposed Course of Project:

Analyses will be completed and findings will be prepared for publication.

Honors and Awards: None

Publications: None

Serial No. M-P-P-(C)-44
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Psychodynamic and Instrumental Learning Models: Implications for Personality Theory and Psychotherapy

Provious Serial Number: None

Principal Investigator: Stanley I. Greenspan, M.D.

Other Investigators: None

Cooperating Units: School and Residence--Hillcrest Children's Center, Children's Hospital, Washington, D. C.

Man Years

Total:	1.34
Professional:	1.00
Other:	.34

Objectives:

1. To develop an internally consistent model of personality (development and organization) based on instrumental learning theory and psychodynamic theories.

2. To test the utility of the integrated model as an aid to: (a) providing a conceptual basis for examining change in psychotherapy; (b) facilitating differential diagnosis and treatment of children and adolescents; (c) designing an effective classroom milieu in a traditional school setting; and (d) aiding psychotherapy in a residential child treatment setting.

Methods Employed:

Formulation of an integrated model representing critical variables affecting human behavior. Utilizing these concepts in establishing a therapeutic milieu in the treatment center, and an environment conducive to learning in a classroom. Pilot studies of the clinical and educational effectiveness of this approach were conducted with the aid of a psychotherapy team and of educators.

Major Findings:

No firm conclusions are warranted at this time regarding the effectiveness of the derived techniques; however, the applicability of the model to the educational and treatment setting has been demonstrated. The model was translatable into operational terms and was successfully communicated to the staffs of the two centers. The treatment plan, derived from the integrated model, appeared to be effective in aiding the treatment of a child who had previously been described as "resistant to treatment."

The consideration of this model together with educators suggests that it is useful in the joint conceptualization of educational and mental health aspects of the school setting. Specific recommendations for research projects on classroom structure to test this and other models are being considered.

Scientific Significance to Mental Health Research Program:

Theories which focus on environmental determinants of behavior and theories which focus on intrapsychic determinants of behavior have each made important contributions to our understanding of personality development, organization, psychopathology, and treatment. A more unified model allows conceptualization of both these sets of variables within one model and thereby affords a fuller understanding of these important areas.

Proposed Course of Project:

Further development of the more unified model with special emphasis on its practical applications.

Honors and Awards: None

Publications: None

Serial No. M-P-A-16
1. Laboratory of Psychology
2. Section on Higher Thought Processes
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: A Study of the Means-end Thought Processes in Human Subjects.

Previous Serial Number: Same

Principal Investigator: Edward A. Jerome, Marguerite L. Young

Other Investigators: None

Cooperating Units: Technical Development Section, NIMH, Computer Systems Laboratory, DCRT

Man Years:

Total:	4.00
Professional:	2.00
Other:	2.00

Project Description:

Objectives: It is the purpose of this project to investigate the mental activities that are responsible for resolving problematic situations that arise in the course of the individual's interaction with his environment. Problems arise from imperfect knowledge of the operational regularities of the external systems that are encountered, and resolution of the difficulty is achieved by competent inquiry into these regularities. In order to be effective, the inquiries must be guided or controlled by a set of cognitive principles collectively called heuristic processes. This project has the following objectives: to describe the distribution of heuristic capabilities in various cross-sections of the population, to discover means of facilitating the acquisition of heuristic principles, to find ways of improving the ability to apply such principles, and to participate in the development of a normative theory of effective heuristic structures.

Methods Employed: Standard tests of mental ability are administered for comparison with performances on a variety of computer-controlled system analysis problems developed for this project. A related set of 14 classes of problems called HEPP has been described in previous reports. Two new sets of problems have been developed this year for the new SEL 810B real-time computer config-

uration. The new problems, called ATSEL and ATREC, monitor improved procedures for the selection and reception paradigms of experiments on concept formation. All of these programs implement special controls that were impossible (prohibitively expensive) without the support of a high speed process-control computer.

Major Findings:

1. Concept Formation. A series of attribute identification experiments were completed during the past year. These studies were controlled in real-time by computer programs that interact with the subject's selection. As a result, the amount of information obtained about each solution effort was maximized by preventing the operation of random factors that lead to solution by guessing, thus eliminating an important source of variability not controlled by other investigators in the field. The problems presented were governed by four logical connectives: "or"; "if...then---"; "...if and only if---"; "...or else----." In the psychological literature on concept identification, there has been considerable disagreement regarding the difficulty of these concept rules. Results of the computer controlled studies support the hypothesis that the subjective difficulty of the various concepts, as estimated from performance measures, is in agreement with objective measures of the complexity of the problem spaces generated by the logical connectives. Specifically, the "...or else---" and "...if and only if---" concept rules have an objective problem space of 12 alternatives and are found to be subjectively easier than the "or" and "if...then---" rules which have a problem space of 24 alternatives. This is an outcome often sought but seldom realized by other investigators. The data also suggest that many of the failures to obtain agreement between performance and objective measures of difficulty result from one or both of the following: a) an inadequate index of performance (i.e., using total number of trials or errors to solution); and b) failure to separate the process of eliciting information from the problem of interpreting or evaluating it.

Another study was concerned with estimating the effects of memory strain on attribute identification. Half of the subjects were required to record their selections and information feedback on forms provided for this purpose. The other subjects were not allowed to record this information. Analysis of the number of trials to solve each problem revealed no statistically significant differences between the group with the memory aid and the group that had to remember the same information.

2. Problem Solving in Schizophrenics. Although it has been frequently alleged that the paranoid schizophrenic's mental functioning is better preserved than that of other schizophrenic patients, a number of recent studies cast some doubt regarding the validity of this notion. In a previous study, a small group of paranoid schizophrenics showed a marked inefficiency in problem solving performance as compared to a group of chronic undifferentiated schizophrenics. Before hypothesizing a specific heuristic difference between these two patient categories, it seemed desirable to

conduct a study on larger groups of subjects. This study was completed and it was found that the chronic undifferentiated schizophrenics always obtained better scores on the problem solving task than did the paranoid schizophrenics. It was also found that the paranoid's performance was disrupted by increasing problem size or objective uncertainty and by reversing the information cue which necessitated a change in set. The chronic undifferentiated patients showed losses in score only when problem size was increased. The low scores of the paranoid schizophrenics appeared to be due to a deficiency in a basic heuristic--the ability to deal with sets of objects.

3. Conversion to a New Real-time Process-control Computer. A considerable proportion of the Section's effort has been directed toward conversion to the new NIMH computer system. This has involved the following:

1. Application hardware. The subject-computer interface, i.e., the stimulus-response hardware operated by the subject to communicate with the computer, had to be redesigned and constructed. The section is indebted to Technical Development, IR-NIMH for this work.

2. Application software. All programs that control the experimental environment had to be rewritten. Several new programs designed to support future studies are now in preparation by the section.

3. System software. The Real Time Executive (RTX) of the SEL 810B as delivered by the manufacturer did not have the capabilities needed for the work planned for the system. A good deal of the section's effort has been devoted to planning the development of these capabilities with the Computer Systems Laboratory of DCRT.

Scientific Significance to the Program of Mental Health Research: The importance of effective thinking for mental health cannot be overemphasized, nor can its importance for the development of society in general during this period of technological and social advancement when stability depends upon the effective functioning of the individual in an ever increasing variety of situations. Although the normative approach is more clearly directed toward the ideal of healthy functioning of the individual in society, it must select its direction of emphasis from the results of descriptive studies that identify existing deficiences in performance. If heuristics generality can be substantiated, even only in part, and if heuristic behavior proves amenable to training techniques, it should be possible to improve means-end thinking and to render more effective our concern with the optimum performance of human beings.

Proposed Course of the Project: Subjects will be tested on computer controlled tasks which are now in the process of being prepared for the SEL 810B. Two types of experimental concept formation tasks will be studied using the reception and selection paradigms: 1) attribute identification and 2) rule identification. In the first, the rule (logical operator) is given by instruction and the subject must identify the unknown attributes (e.g., black, square, etc.). In the second, the relevant attributes are given and the rule must be identified by the subject (e.g., conjunction, disjunction, etc.). These studies will employ a two-valued logic and will be extended to n-valued logic in the future.

Honors and Awards: None

Publications: Young, Marguerite L.: Age and sex differences in problem solving. In press.

Serial No. M-P-B-2
1. Laboratory of Psychology
2. Section on Neuropsychology
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Analysis of the relationship between problem-solving behavior and certain cortical and subcortical structures in the sub-human primate brain.

Previous Serial Number: Same.

Principal Investigators: H. Enger Rosvold, Mortimer Mishkin, Patricia Goldman

Other Investigators: Donald Marburg, Ph.D. Candidate, University of Texas NIMH Predoctoral Fellow.
Dr. Lajos Vereczkei, International Research and Exchanges Board, Foreign Exchange Scholar, University Medical School, Pecs, Hungary.
Dr. Roger Buddington, NIMH Postdoctoral Fellow

Cooperating Units: None

Man Years:
Total: 5
Professional: 2 4/5
Other: 2 1/5

Project Description:

Project: To identify the brain structures that are essential for problem-solving behavior.

Objectives: To determine the neural system or systems serving problem-solving behavior as exemplified in delayed-response, discrimination, learning set, etc., and to describe the nature of the behavioral deficits which follow damage to the structures comprising these systems.

Methods: (1) A variety of behavioral tests are used to define the functions which are specific to the prefrontal lobes as a whole, or to various of its parts. The current emphasis is to analyze the frontal-lobe deficit in terms of its participation in spatially directed responses and the utilization of interoceptive and exteroceptive cues. (2) Lesions are being placed in various parts of the prefrontal lobes (principal and arcuate sulci, ventral convexity, orbital surface, premotor area). The current emphasis is to determine the

extent to which each of these areas participates in each factor of the frontal-lobe deficit. (3) Lesions are placed in subcortical structures (caudate nucleus, centrum medianum, medialis/hypothalamus) and the effects compared with those following selective frontal lesions as in (2).

Major Findings: (1) Earlier work had suggested that the deficit in monkeys following dorsolateral prefrontal cortical lesions is due to a disturbance in utilization of response-induced (as opposed to stimulus-induced) cues when responding to spatial factors in a test. A study has been designed to test this directly in a locomotor maze situation in which it will be possible to distinguish between the two sources of error. Results are not yet available. (2) The effects of fractional prefrontal lesions were compared on delayed response and place reversal, two tests which contain both a spatial and a mnemonic factor, and on go - no go alternation, a test which involves only the delay factor. On the tasks which contained both factors, lesions of the principal sulcus resulted in impairments which were nearly as severe, and in some cases, just as severe as those produced by removal of the entire dorsolateral region, while lesions of the arcuate sulcus were either far less effective or totally ineffective in disrupting performance on these tasks. By contrast, when comparisons were made on tests which involve only the delay factor, as in the go - no go alternation test, or only the spatial factor, as in a conditional position response test studied previously, the tests were no longer sensitive to the disorder produced by removal of the principal sulcus but rather to that produced by ablation of the arcuate cortex. The results from these experiments indicate that lesions of the dorsolateral prefrontal cortex produce two dissociable disorders, the one classically associated with the frontal lobes having its cortical focus in the principal sulcus, and the other, as yet poorly understood, with its focus in the arcuate sulcus. These studies of small lesions on a variety of spatial and non-spatial tasks have revealed an unanticipated specialization within the dorsolateral region and thus have dispelled the prevalent conception of a unitary dorsolateral mechanism. They have also provided insight into the nature of the classical deficit in terms of a loss in immediate memory for spatial information. The notion of a modality-specific memory loss produced by prefrontal lesions is in the tradition of Jacobsen's formulations earlier in the century and is not unlike the more recent proposal of "gnostic" areas by Konorski. Until now, and in general, however, the significance of memory in prefrontal deficits had been largely ignored. (3) Earlier work had demonstrated that those functions which are differentially affected by dorsolateral and orbital cortical lesions are also differentially affected by lesions in subcortical structures which receive anatomical projections selectively from the dorsolateral or orbital frontal cortex. Anatomical and electrophysiological studies have demonstrated that the centrum medianum nucleus is a subcortical structure related principally, though not exclusively, to the orbital frontal system, suggesting that lesions in this subcortical structure would affect primarily orbital functions. In a study testing this possibility it was found that lesions in the centrum medianum do not affect performance on tests indicative of dysfunction in either the lateral or the orbital system; they do, however, raise the threshold for reaction to pain, an effect often associated with

lesions in limbic system areas of the frontal lobe. Another study is underway to examine whether or not cognitive functions are affected by hypothalamic lesions, and whether or not the functions of different areas of the hypothalamus may be dissociated on the basis of their differential connections with the cortex. In different groups of monkeys, lesions have been placed selectively in the anterior, lateral, or medial hypothalamus and are being tested on visual pattern discrimination, spatial delayed alternation, and object reversal tests, tests which distinguish between the effects of dorsolateral and orbital frontal lesions. Preliminary results suggest that operated animals regardless of location of lesions are impaired on all tests. If this is confirmed in additional animals, it will have to be concluded that the differential projections from the cortex to the hypothalamus are irrelevant for the behavior examined in these tests and that the hypothalamus enters into cognitive behavior non-specifically, probably contributing a general motivational factor.

Scientific Significance to Mental Health: The results of this project have revealed that the prefrontal cortex in monkeys is functionally heterogeneous with dorsal and ventral areas participating in problem-solving behavior in two quite different ways; even within these areas there is evidence of further specialization of function. Furthermore, each of these frontal areas appears to be but one component of a larger cortical-subcortical system. Specification of the types of cortical contributions to problem-solving, and delineation of the two cortical-subcortical systems, should help to resolve the long-standing puzzle regarding the functions of the frontal lobes.

Proposed Course of Project: No major shift in emphasis is anticipated.

Honors and Awards: None

Publications:

Goldman, Patricia S. and Rosvold, H. E. Localization of function within the dorsolateral prefrontal cortex of the Rhesus monkey. Experimental Neurology 27: 291-304, 1970

Goldman, P. S., Rosvold, H. E., Vest, B. and Galkin, T. W. Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the rhesus monkey. J. comp. physiol. Psychol., In Press, 1971.

Iversen, S., and Mishkin, M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Experimental Brain Research, 11: 376-386, 1970.

Marburg, D. L. Behavioral effects of ablation of the centromedian nucleus in the thalamus of the Macaca Mulatta. Unpublished doctoral dissertation, Department of Psychology, The University of Texas at Austin, 1971.

Waxler, M., and Rosvold, H. E. Delayed alternation in monkeys after removal of the hippocampus. Neuropsychologia, 8: 137-146, 1970.

Serial No. M-P-B-5
1. Laboratory of Psychology
2. Section on Neuropsychology
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Neural mechanisms in vision.

Previous Serial Number: Same

Principal Investigator: Mortimer Mishkin

Other Investigators: Lillian Blake (Consultant Part-time)
Marvin Snyder (NIMH Senior Staff Fellow)

Cooperating Units: Charles Gross, Princeton University, Cambridge.
Frederick J. Manning, WRAIR, Washington, D. C.

Man Years:
Total: 4 3/5
Professional: 1 4/5
Other: 2 4/5

Project Description:

Project: Behavioral, anatomical, and electrophysiological analysis of neural mechanisms in vision.

Objectives: To define the role in vision of neural structures outside the primary visual projection system.

Methods: (1) Monkeys are prepared at NIMH with various lesions to the visual system, and they are then studied electrophysiologically at Princeton University by Gross and his colleagues to determine whether or not the receptive field properties of inferotemporal units have been altered in a manner predicted by our theory of cortico-cortical transmission. (2) Monkeys are trained before and after tectal, pretectal, or posterior thalamic lesions on a spatial or a difficult non-spatial visual discrimination task as a step toward determining whether the superior colliculus - posterior thalamus - extrastriate cortical projection might be concerned with spatial as opposed to object or pattern vision. (3) Monkeys are trained after various lesions of the limbic system on visual associative learning tasks as a step toward determining whether direct interaction between the visual and limbic systems might be the mechanism whereby visual stimuli gain emotional/motivation significance for the animal.

Major Findings: (1) In accord with predictions, left striate cortex ablation restricts the receptive zones of inferotemporal units in both hemispheres to the left visual field, while forebrain commissurotomy limits the receptive zones of inferotemporal units to the visual field contralateral to the hemisphere being recorded from (i.e., the left field for right inferotemporal units, and the right field for left). (2) The monkeys are currently being trained on the discrimination tasks prior to receiving lesions to visual structures outside the geniculo-striate system. (3) Both orbital frontal and temporal pole plus amygdala lesions (but not hippocampal lesions) impaired object reversal learning, suggesting that anatomical interconnections between the visual system and these two parts of the limbic system may indeed participate critically in the formation of stimulus-reward associations.

Scientific Significance to Mental Health Research: Vision is perhaps the best understood of the sensory modalities in relation to the functioning of the nervous system. Yet a major problem remains unsolved in vision as it does in all sensory modalities: Delineation of the events which intervene between stimulus reception at the cortex and the observed response. The demonstration that damage to the inferior convexity of the temporal lobes in monkeys produces impairment in visually-guided behavior has opened up the hitherto inaccessible area of the intracerebral processes in vision, i.e., neural activity related to vision but beyond the level of the striate cortex. Unravelling these mechanisms in vision should aid greatly in the solution of a general problem for psychology, viz., accounting for the intervening neural processes (thought and its breakdown) in normal and abnormal behavior.

Proposed Course of Project: (1) Monkeys with pulvinar, bimacular striate, and prestriate lesions are currently being added to the electrophysiological study in order to test the theoretical neural model in greater detail. (2) Animals are being trained on the spatial and nonspatial tasks preliminary to electrocoagulation of tectal and pretectal areas.(3)A study is being planned, dealing with visual evoked potentials in the limbic system during visual associative learning, in order to pursue the issue raised by the results of limbic-ablation experiment.

Honors and Awards: None

Publications:

Mishkin, M. Cortical visual areas and their interactions. In A. Karczmar & J. C. Eccles (eds): The Brain and Human Behavior, Springer-Verlag. In Press.

Snyder, M. The evolution of mammalian visual mechanisms. In R. Jung (ed): A Handbook of Sensory Physiology, Springer-Verlag. In Press.

Serial No. M-P-B-7
1. Laboratory of Psychology
2. Section on Neuropsychology
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Histological analysis of cerebral lesions and intracerebral connections in primates.

Previous Serial Number: Same

Principal Investigator: H. E. Rosvold and M. Mishkin

Other Investigators: T. N. Johnson (Consultant-part-time)
Marvin Snyder (NIMH Senior Staff Fellow)

Cooperating Units: None

Man Years:
Total: 2 4/5
Professional: 4/5
Other: 2

Project Description:

Project: Verification of lesions in chronic experimental animals, and analysis of intracerebral connections in acute preparations.

Objectives: The objective of the first part of this project is to delineate the loci of the lesions which produce specific behavioral effects, and of the second, to determine whether or not loci yielding similar effects are anatomically interconnected.

Methods: When the behavioral testing of chronic experimental animals is completed, their brains are embedded in either celloidin (large specimens) or paraffin (smaller specimens), sectioned, stained for cells and fibers, examined microscopically, and the lesions reconstructed. In the second part of the project, animals are prepared with selective lesions purely for anatomical investigation. The animals are sacrificed within a few days after surgery and their brains examined microscopically to determine the locus, extent and course of degenerating fibers. Special staining procedures and fiber-size determinations are used to study stage of myelinization.

Major Findings: Specimens completely processed and examined include 120 monkey brains. This material has been examined for the purpose of verifying the loci of the cortical and subcortical lesions in animals used for behavioral studies.

In previous studies it had been demonstrated that there is a topographic projection of fibers from various parts of the frontal cortex to the head of the caudate nucleus and the putamen. More recently we have demonstrated that this topographic arrangement is maintained in the efferents from the caudate and the putamen to the globus pallidus and the substantia nigra. In the globus pallidus, the fibers from the anterodorsal caudate take a lateral position, while those from the ventrolateral caudate take a medial position, fibers from putamen take a ventral position while those from the caudate take a dorsal position. It is known that each of these parts of the pallidum, in turn, projects to different structures; the lateral part to the subthalamus, the medial part to the thalamus. Thus, there are at least two systems, one consisting of dorsolateral frontal cortex, anterodorsal caudate, lateral pallidum, and subthalamic nucleus; the other, consisting of orbital frontal cortex, ventrolateral caudate, and thalamus. Projections to the substantia nigra from the precommisural neostriatum are confined to the most rostral portions of the reticulata compacta.

Lesions were placed in the superior colliculus of monkeys in order to determine whether the secondary visual pathway present in the rat, cat, tree shrew, and squirrel is also present in the higher primates. Preliminary results indicate that the superior colliculus of the rhesus monkey projects to the inferior pulvinar, a connection which appears to be homologous to that reported in non-primate mammals. The inferior pulvinar, in turn, has its major projection to the prestriate cortex. In addition, degeneration after the colliculus lesions was traced to the posterior portion of the reticular nucleus and the nucleus centralis lateralis. Continuing studies of the midbrain visual system have involved the pretectal area. Preliminary evidence indicates that the pretectum projects to the lateral posterior nucleus. This opens up the possibility of yet another visual pathway to the neocortex since the lateral posterior nucleus projects to the parietal neocortex.

Scientific Significance to Mental Health Research: Sufficient evidence has been accumulated in behavioral studies with brain damaged animals to suggest that widely separated cell aggregates in cortex and subcortex may be combined into a complex system; and it is the functioning of such neural systems, rather than the functioning of the particular elements of which they are composed, that seems most directly relevant to an understanding of the organization and disorganization of behavior. The significance of this project lies in the fact that it can provide detailed information on the composition of these neural systems; systems which through electric and chemical manipulation have been related to mental health and disease.

Proposed Course of Project: No major shifts in emphasis are contemplated.

Honors and Awards: None

Publications: None

Serial No. M-P-B-14
1. Laboratory of Psychology
2. Section on Neuropsychology
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project title: The neural regulation of appetitive behavior.

Previous Serial Number: Same

Principal Investigator: H. Enger Rosvold

Other Investigators: Douglas Bowden (University of Washington, Seattle)

Cooperating Units: None

Man Years:
Total: 2/5
Professional: 1/5
Other: 1/5

Project Description:

Project: To identify the brain structures which are involved in food-oriented social behavior.

Objectives: The objective is first to identify structures in the brain which are related to food and water oriented behavior, then to obtain an understanding of how food regulating mechanisms in the brain determine the social behavior of monkeys.

Methods: The brain is first explored with roving electrodes for sites which regulate drinking behavior when stimulated while the animal is restrained. When such structures are located, the effect of stimulation in these areas was examined with respect to various degrees of thirst motivation and the reliability of the effects over length of time of stimulation.
Four monkeys were implanted with a total of 80 chronic electrodes in brain areas where electrical stimulation elicits drinking. All of the histological analysis has been completed and the behavioral data has been analyzed.

Major Findings: The effect of stimulation in areas which elicit drinking was examined with respect to the various degrees of thirst motivation and the reliability of the effects over length of time of stimulation. It was found that some animals drink to brain stimulation, others do not, even though the same brain areas are stimulated. In those animals that drink to stimulation, the volume of the brain system mediating the response increased during the six weeks of stimulation for drinking points; i.e., a greater proportion of sites gave rise to the response as the exploration for sites proceeded. In

non-drinkers, the anatomical system from which drinking could be elicited became smaller. Within animals, the relationship between self-stimulation and drinking elicited from selected points was consistent from point-to-point, but the kind of relationship differed for the two animals which were studied in this regard. The interpretation being placed on these data is that activity in at least some cells of the hypothalamus motivates behavior only in a general sense until physiological and/or environmental conditions are such as to shape specific behavior patterns. Furthermore, these cells can be committed to other functions should the conditions change.

Scientific Significance to Mental Health Research: Understanding the motivation of behavior is fundamental to an understanding of both normal and abnormal behavior. It is anticipated that this study will contribute to an understanding of the brain's participation in motivation.

Proposed Course of Project: Project will terminate with publication of results. No further research on this project is possible due to reduction in staff.

Honors and Awards: None

Publications: None

Serial No. M-P-B-15
1. Laboratory of Psychology
2. Section on Neuropsychology
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The brain's participation in social and emotional behavior.

Previous Serial Number: Same

Principal Investigator: H. Enger Rosvold and Patricia S. Goldman

Other Investigators: Douglas Bowden (University of Washington, Seattle)

Cooperating Units: None

Man Years:
Total: 2/5
Professional: 1/5
Other: 1/5

Project Description:

Project: To establish which brain structures and functions participate in social and emotional behavior.

Objectives: The objective is to identify the different ways in which different parts of the brain regulate emotional and social behavior.

Methods: In one part of this study one-year old monkeys which sustained lesions in dorsolateral or orbital prefrontal cortex or in the head of the caudate nucleus at 50 days of age were studied in groups of two or three and then individually when the groups were broken up. In another part of the study three-year old monkeys which have lived together in pairs for one year were separated and the effects of separation on emotional behavior observed. Closed-circuit television and video recorder have permitted remote observation and frequent play-back of observations. Techniques for establishing inter-observer reliability in recording behavior have been developed and computer programs for processing the data are in preparation. Remote sensing devices are being used to detect psychomotor retardation, loss of appetite, and sleep disturbance.

Major Findings:

Social and emotional behavior in brain lesioned infant monkeys:

More than 50 different behaviors were studied by time-lapse video recordings in thirteen one-year old monkeys in which either dorsolateral or orbital

prefrontal cortex or head of caudate nucleus had been removed from their brains when they were 50 days old. They were observed first in their home cages in stable living groups which had existed for at least 6 1/2 months and then again immediately after they had been separated from one another. The major results indicated that monkeys with orbital lesions differed from unoperated controls in more ways than did the dorsolateral monkeys; when they were in groups, the animals with orbital lesions slept more and were more sedentary even when awake; when they were living singly, by contrast, they became hyperactive and spent most of their time in locomotion. These findings lend support to the notion, derived from studies of cognitive behavior in infant operated monkeys, that functions of the orbital frontal cortex, unlike those of the dorsolateral frontal cortex are not spared following brain damage in infancy. Further, the nature of the behavior exhibited by impaired monkeys led to the suggestion that the orbital cortex may play an important role in modulating arousal mechanisms in the infant and the adult monkey alike.

Separation Stress in Primates:

Five pairs of 2-year old monkeys which lived together for six to nine months were separated and observed two weeks for changes in activity level, for appetite, and sleep (i.e. "depression syndrome"). Time-lapse video recordings were obtained to provide information as to changes in the frequencies of over 50 different categories of behavior. The pairs were then reunited and observed for five days in order to compare the response to reunion with that to separation. There were no clear changes in activity level, appetite, or sleep cycles suggesting that either indicators of depression are not apparent in adolescents separated from their peers or that this method is insensitive to such changes in these older age-groups. Upon separation all animals showed an initial increase in the frequency of many responses which was followed by a relatively inactive period characterized by rocking and own-body oriented behavior. Upon reunion there was an initial period of excitement characterized by considerable sexual activity and aggressive behavior.

Scientific Significance to Mental Health Research: Mental health results in acceptable social adjustment. Mental disease is apparent first in a breakdown of one's interactions with his fellows. It is anticipated that this study will contribute towards an understanding of the brain's participation in social interactions, and provide a subhuman primate model for studying mental disease.

Proposed Course of Project: Project will terminate with publication of results. No further research on this project is possible due to reduction in staff.

Honors and Awards: None

Publications:

Bowden, D. M., Goldman, Patricia S., Rosvold, H. E. and Greenstreet, R. Free behavior of rhesus monkeys following lesions of the dorsolateral and orbital prefrontal cortex in infancy. Experimental Brain Research, 12, 1971.

Serial No. M-P-B-16
1. Laboratory of Psychology
2. Section on Neuropsychology
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Cerebral mechanisms underlying functional plasticity in the developing organism.

Previous Serial No.: Part of M-P-B-2

Principal Investigator: Patricia S. Goldman

Other Investigators: H. Enger Rosvold
Epp Miller (NIMH Postdoctoral Fellow)

Cooperating Units: None

Man Years:
Total: 3 3/5
Professional: 1
Other: 2 3/5

Project Description:

Project: To determine the cerebral mechanisms underlying functional plasticity in the developing organism.

Objectives: Behavioral deficits following cortical injury are commonly less severe the earlier in life the injury is sustained. The major purpose of this research is to understand the mechanisms by which recovery is accomplished following brain damage in infancy and to determine whether or not similar mechanisms could be enhanced or induced when such damage is sustained later in life.

Methods: The studies involve the comparison of identical lesions in infants and juveniles. The infants are usually operated when they are 2-months of age; the juveniles between 1 1/2 and 2 years old. Both groups are allowed a 10-month postoperative recovery. Thus, the infants are 1-year of age and the juveniles 28-34 months old when formal testing of their cognitive abilities is begun. Unoperated monkeys of the same ages (that have also resided in the laboratory for ten preceding months) are tested as well. The studies have involved the following lesions: prefrontal lobectomies; dorsolateral prefrontal and orbital prefrontal resections; caudate nucleus lesions; combined prefrontal lobectomies and caudate lesions; and ablation of the dorsomedial nucleus of the thalamus.

The behavioral tests utilized are designed to measure specific and dissociable functions of the prefrontal cortex. The same tests are given in the same order to infants and juveniles alike. Upon completion of the testing, which may require a year or longer, the monkeys are sacrificed and their brains processed for histological examination

Major Findings: In the adult monkey, selective removal of the dorsolateral cortex produces an irreparable loss in the ability to perform spatial delayed responses. If the dorsolateral cortex is removed in infancy, however, delayed-response ability is preserved to a remarkable degree. The early studies in this laboratory began by searching for a cortical area in the infant the removal of which, when added to the original lesion, would prevent recovery of delayed-response abilities. Such an area would presumably have mediated the recovery observed following the dorsolateral lesion alone. Since the orbital prefrontal cortex, like the dorsolateral prefrontal cortex, receives projections from the dorsomedial nucleus of the thalamus, and moreover, is implicated in delayed-response performance, this area together with the dorsolateral cortex was removed in 2-month old monkeys. Rather than supporting the idea that the orbital cortex was essential for recovery, the results of this and subsequent studies indicated that dorsolateral and orbital prefrontal cortex differ in the degree to which their respective functions can be recovered following early removal. While functions of the dorsolateral cortex were restored following early brain damage, those of the orbital cortex were not. Moreover, the deficits following orbital removal in infancy were just as severe as those following orbital removal later in life. The evidence for differential sparing of function, together with the hypothesis that recovery occurs only if the cerebral function has not yet developed at the time of surgery, suggested that orbital prefrontal cortex becomes functional earlier in ontogeny than does dorsolateral prefrontal cortex. Studies completed this year firmly support this idea and provide new information about the plasticity problem. The new information pertains to the question of whether or not orbital function can be recovered at still later stages of development than those at which the primary loss was determined. Initially, it had been assumed that recovery, to the extent that it was possible, would occur by the time the monkey was a year or so old. It turns out, however, that orbital function can be restored-but not until the monkey reaches at least two years of age. All of the monkeys in the current studies were first tested for delayed alternation ability, for example, when they were fifteen months of age. The monkeys with orbital lesions in infancy were severely impaired at that stage of development, whereas monkeys given dorsolateral lesions in infancy were not. Both groups were retested for delayed alternation ability when they were 24-months of age. At this time, all of the orbital monkeys were able to perform the task within normal limits; the retest performance of the dorsolateral group was more variable - half of the group performed normally as before, but half failed to relearn. The data suggested that whereas the orbital monkeys clearly improved with age, the dorsolaterals showed a tendency to deteriorate. If orbital cortex develops earlier in ontogeny than dorsolateral cortex, as earlier work indicates, it is possible that dorsolateral cortex may mediate the recovery of orbital function when time is allowed for the functional elaboration of this later

developing area. The data also suggest that this compensatory relationship may not be reciprocal, i.e., that orbital cortex cannot subserve dorsolateral function following dorsolateral injury in infancy. The dramatic evidence for sparing of dorsolateral function at the 15-month stage may then reflect the functional immaturity of this region at that age, so that its removal is without effect, rather than a process of reparation as previously envisioned. The idea emerging from these studies is that recovery of function will be possible only when two criteria are fulfilled: (1) the cortical areas remaining intact at the time of surgery are functionally related to the damaged area; and (2) the remaining areas are not already "committed" to their ultimate organization at the time of surgery. Such a formulation could explain why some cortical lesions in infancy result in behavioral sparing while others do not; it also provides a clue to the essential difference in the capacity of infant- and adult-brain damaged cases for recovery of function. Only in infants would there be the possibility of "uncommitted" areas remaining after injury.

Scientific Significance to Mental Health Research: By understanding mechanisms for recovery of function following neonatal injury, we may be in a better position to correct errors of normal development as well as approach the problem of recovery in the adult-brain injured.

Proposed Course of Project: On the basis of behavioral studies it is possible to infer certain anatomical consequences of neonatal injury. An attempt will will be made in the years ahead to find evidence of new connections in early-lesioned animals, formed perhaps by the sprouting of intact collateral axons, which could provide the anatomical basis of plasticity in developing organisms.

Honors and Awards: None

Publications:

Goldman, Patricia S., Rosvold, H. E., and Mishkin, M. Selective sparing of function following prefrontal lobectomy in infant monkeys. Experimental Neurology, 29: 221-226, 1970.

Serial No. M-P-L-5
1. Laboratory of Psychology
2. Section on Perception
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Individual Differences in Normal Perceptual Processes

Previous Serial Number: Same

Principal Investigator: V. R. Carlson

Other Investigators: E. P. Tassone

Cooperating Units: None

Man Years: None

Project has been temporarily discontinued.

Serial No. M-P-L-7
1. Laboratory of Psychology
2. Section on Perception
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Perceptual Adaptation

Previous Serial Number: Same

Principal Investigator: V. R. Carlson

Other Investigators: Irwin Feinberg, Donald Goodenough, Eugene Tassone

Cooperating Units: Fort Miley VA Hospital, San Francisco
Downstate Medical Center, New York City

Man Years

Total:	2.5
Professional:	2.0
Others:	.5

Project Description:

Objectives: To investigate the characteristics of perceptual adaptation, both when the adaptation occurs in a single limited period of persistent stimulation and when it is cumulative in a series of stimulations over relatively long periods of time.

A basic problem in the investigation of perceptual adaptation is the role of the perception of time itself, whether changes in time sense are a cause or an effect of adaptational change. The predominant view is that the subjective rate of the passage of time is dependent upon the events and factors determining the state of the organism at any given time. Changes in such factors as metabolic rate and neural activity of the brain associated with the circadian cycle have figured most prominently in theories of the origin of the time sense. We sought to determine whether the perceived rate of passage of time does in fact vary during the circadian cycle.

Methods Employed: In one experiment subjects were awakened at intervals of 45-60 minutes during the night and tested briefly on their ability to estimate the duration of short time intervals (1-10 sec.). In another experiment subjects were similarly awakened periodically but were asked to estimate the time that had elapsed since the previous awakening. Subjects were also tested before retiring and after awakening in the morning. EEG activity was continuously recorded throughout the night.

Major Findings: Significant differences in time judgment did not emerge between the estimates made during the night and those made before retiring and upon awakening the next morning. Nor did the time judgments vary significantly as a function of the kind of EEG activity preceding the judgments. If one thinks in terms of an "internal clock," there was some indication that the rate of such a clock tends to decrease and then increase over the course of a night's sleep. In previous experiments, however, we have found such an effect associated with repeated day-to-day testing occurring in the normal daytime awake condition.

Scientific Significance to Mental Health Research Program: These results indicate that time perception may be largely independent of the circadian rhythm and may represent a much more essential process underlying stable perception of the external world than is generally supposed. An important question, for example, is whether anomalies in time sense, such as occur in schizophrenia, give rise to disordered perceptions of cause and effect relationships, or whether disordered thought processes produce the abnormal time perceptions.

Proposed Course of Project: Since the trend in the apparent rate of the passage of time over the night was similar to the day-to-day trend, both may be due to a practice effect unrelated to the circadian cycle. It is therefore necessary to determine whether the trend over a single day of normal waking activity is similar to or different from that occurring over the night.

Honors and Awards: None

Publications:

Carlson, V. R., and Feinberg, I.: Time judgment as a function of method, practice, and sex. J. Exp. Psychol. 85(2): 171-180, 1970.

Serial No. M-P-L-9
1. Laboratory of Psychology
2. Section on Perception
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Discriminative and Conceptual Behavior in Preschool Children

Previous Serial Number: Same

Principal Investigator: Albert J. Caron

Other Investigators: None

Cooperating Units: Private and Cooperative Nursery Schools in Montgomery County and the District of Columbia.

Man Years: None

This project was temporarily suspended and is being held in abeyance.

Honors and Awards: None

Publications:

Caron, A. J.: Discrimination shifts in 3-year-olds as a function of shift procedure. Develop. Psychol. 3(2): 236-241, 1970.

Serial No. M-P-L-10
1. Laboratory of Psychology
2. Section on Perception
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Discriminative and Conceptual Behavior in Infancy.

Previous Serial Number: Same

Principal Investigator: Albert J. Caron

Other Investigators: Rose F. Caron

Cooperating Unit: Eye Research Foundation

Man Years:

Total:	1.25
Professional:	.75
Others:	.50

Project Description:

Objectives: To assess the discriminative capacities of human infants and to investigate the antecedent factors affecting early perceptual and intellective development.

Study I: The specific aim of a study now in progress is to determine which features of the human face (eyes, nose, mouth, hair, contour) are most salient for the four-month-old and whether these are perceived as isolated elements or as structured configurations.

Methods Employed: Infants between 112 and 126 days were randomly assigned to fifteen experimental groups with the single restriction that 4 males and 4 females appear in each group. All subjects were given six 30-second repeated exposures of a distorted version of a female schematic face, following which they received a 30-second exposure of the regular female schematic face. Looking time to each picture was determined by the pupilary reflection technique, only those infants whose total looking time declined 25% or more during repetition being retained as subjects. The experimental groups differed in terms of the type of facial distortion presented during the repetition trials. One portion of the groups saw distortions of the total face (upside down face, upside down features--right side up contour, upside down contour--right side up features, symmetrically scrambled features, asymmetrically scrambled features); a second portion saw distortions of the

eyes only (eyes absent, both eyes scrambled, one eye scrambled, eyes vertically arranged in center of forehead, eyes in normal arrangement but lowered to mouth level); and finally a third portion received distortions of the nose-mouth or hair only (hair absent, nose-mouth absent, nose-mouth scrambled, nose-mouth horizontally arranged under eyes). A control group saw the regular schematic face during the repetition trials. The critical measure was total looking time to the regular face following repetition. Presumably, the longer the looking time, the more different the face was perceived from the previously habituated face.

Major Findings: Though the study is not yet completed, the preliminary data indicate that the eyes are more critical than the nose-mouth or hair in the face perception of the four-month-old. Right-side-up orientation is also important whether of features, contour, or both. Finally, the eyes are structured not as a pair, but as an element which appears laterally in the upper portion of the face.

Study II: The purpose of a second infant study, which has just been initiated is to determine whether the three-month-old has achieved perceptual object constancy, i.e., whether objects seen at different perspectives retain their identity for him.

Methods Employed: An apparatus has just been constructed which will allow us to train infants on operant discriminations. Thus, three-month-olds will be trained to make a small left head-turn (18^{o}) in the presence of a standard circle (for which they will be contingently reinforced with simulated peek-a-boo faces and music) and to make a right head-turn (18^{o}) in the presence of an ellipse. Following training, the infants will be tested with a circle tilted so that its retinal image is identical to that of the ellipse. If the tilted circle is seen retinally, they should turn to the right; if it is seen objectively, they should turn to the left. The experiment will also be repeated with rectangles and trapezoids.

Major Findings: Currently, we are piloting infants on discrimination training, trying to obtain an optimal reinforcement package and the optimal amount of intermittency of reinforcement to insure discriminative learning. Since no one has yet successfully trained infants of this age to discriminate, this part of the study will itself be a contribution.

Scientific Significance to Mental Health Research Program: Both studies, taken together, will give us some insight into the perceptual achievements of young infants. The face study will tell us what features predominate in the baby's perception of the human face and the extent to which these features have been structured into stable configurations. The object constancy study will tell us whether the infant has yet been able to structure a stable object world or sees a continually changing, "retinal" world. Should it turn out that the infant's world is structured, a further implication is that this has been attained prior to extensive movement in the environment and hence that the development of visual perception is primarily an achievement of the eye rather than of the hand or the kinaesthetic senses.

Proposed Course of Project: This project is an indefinitely continuing one in pursuance of the general objectives stated above.

Honors and Awards: None

Publications:

Caron, R. F., Caron, A. J., and Caldwell, R.: Satiation of visual reinforcement in young infants. Develop. Psychol., 1971, in press.

Serial No. M-P-L-12
1. Laboratory of Psychology
2. Section on Perception
3. Bethesda

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Cortical Mechanisms in Somesthesis

Previous Serial Number: M-P-B-12

Principal Investigator: Josephine Semmes

Other Investigators: Mary Randolph (NIMH Special Fellow)
Louis Porter (NIMH Predoctoral Fellow)
Robert Schwartzman (Clinical Neurology Branch)

Cooperating Units: Clinical Neurology Branch

Man Years
Total: 5
Professional: 3
Other: 2

Project Description:

Objectives: The general aim is to identify in monkeys the neural mechanisms concerned in manual (tactual and kinesthetic) discriminations of various types.

It is generally held, on the basis of classical neurological teaching and of modern electrophysiological studies, that the main cortical projection fields of the dorsal column-medial lemniscus system (Somatosensory Areas I and II) are essential for all kinds of fine discriminative sensation. By contrast, the extra-lemniscal projections to the cortex (which are more widely dispersed) are regarded as serving only the cruder aspects of sensation, perhaps mainly nociceptive. Behavioral tests in animals with verified lesions are needed to confirm or deny this hypothesized functional distinction between the lemniscal and the extra-lemniscal somatosensory systems.

Methods: In the original battery of tests, monkeys were trained to make somesthetic discriminations in a situation requiring them to reach with one hand into an opaque box and select one of two stimulus objects. The differentiating characteristics of the objects had to be perceived by the monkey using active palpation. Discrimination tasks of consistency, shape, size, roughness, and temperature were employed, and for the last three, repeated determinations of thresholds were made. This experimental situation requiring "active touch" continues to be used but has now been supplemented by another involving merely "passive touch." In the passive situation, the monkey is restrained in an opaque box with the hand to be tested extending through an aperture and held flat on a platform by straps. The instrumental response,

pushing open a hinged door in the box when the animal detects the positive stimulus (e.g., a touch), is performed with the non-stimulated hand. With this technique, thresholds of the palm to light tactual stimuli (modified von Frey hairs) have been determined. A series of nylon monofilaments, calibrated according to the force exerted when bent against a surface, is used. Thresholds are determined repeatedly before and after operation until a consistent level of performance is reached. These two types of situations, the "active" and the "passive," are further supplemented by frequent neurological examinations.

Ablations of cortical areas are made by aspiration of grey matter, with aseptic technique and barbiturate anesthesia. The postoperative recovery period is usually four weeks, after which tests and retraining are begun. Following completion of the behavioral part of the experiment, the animals are given a lethal dose of barbiturate, and their brains are prepared for histological examination. The actual limits of the cortical lesion and the consequent thalamic degeneration are then determined.

Major Findings: The effects of four equal-sized adjacent lesions of the sensorimotor hand representation in the central gyri were compared: anterior precentral, posterior precentral, anterior postcentral, and posterior postcentral. A sharp functional distinction was found between the precentral and the postcentral lesions, i.e., the two precentral removals did not impair discrimination performance at all, whereas the two postcentral removals did produce such impairment. This finding was unexpected, since it has long been supposed by previous investigators that the precentral gyrus (because of its afferent inflow) was at least secondarily involved in somatosensory discrimination. In the present study, a clear (although not an absolute) distinction was also found between the two postcentral removals: the anterior lesion produced a severe impairment on all the active discrimination tasks except temperature, whereas the posterior ablation of the gyrus was followed by deficit only on the difficult shape discriminations. Since the anterior postcentral region receives a heavier input from the thalamus than the posterior portion of the gyrus, these results were in the expected direction, although the deficits after this lesion were more severe than those obtained by others. From several lines of evidence gathered by us, it appears most likely that the reason for the difference was that our lesions were more complete in the depths of the central sulcus than those made by previous investigators. The reason for the deficit which selectively affected the difficult shape discriminations as a result of the posterior postcentral lesion is also challenging and must be explored further in the attempt to discover its basis.

The data from the 4-lesion experiment, which indicated clearly that the anterior postcentral removal produced a more extensive and severe deficit than any of the others, prompted attempts to define the sensory deficit after this restricted ablation more precisely. On neurological examination, monkeys with anterior postcentral lesions show long-lasting deficits in cortical reflexes (placing and hopping) and an abnormal resting posture of the upper limb. However, they are not deficient, at least to gross observation, in comparing the discriminanda and in performing the instrumental response re-

quired in the formal "active touch" problems. It should be noted that their excellent performance on temperature discrimination serves as a control for all the aspects of the "active" situation except the nature of the discriminada themselves. In the "passive" situation, they retain or recover normal thresholds to punctate tactual stimuli, indicating that sensitivity to contact *per se* is not at fault. Tactual acuity (two-point discrimination) has turned out to be only slightly impaired, and thus this deficit also seems insufficient to account for the monkeys' extremely poor performance on the various active two-choice discriminations, some of which employed grossly different stimulus objects (e.g., metal vs. foam rubber covered cylinders).

The deficit after the anterior postcentral ablation was explored further by subdivision of this lesion into two: the bank of the central sulcus (roughly corresponding to cytoarchitectural area 3) and the crown of the gyrus (roughly approximating area 1), since, contrary to what was previously thought, it has recently been found (by electrophysiological studies) that the hand and fingers are completely represented in each of these areas. The behavioral results revealed that removal of the "area 3" subdivision was mainly responsible for all the deficits found after the original lesion, although a slight deficit on two of the tests also followed removal of the "area 1" subdivision. Microelectrode mapping of the presumably intact "area 3" or "area 1" cortex in the operated monkeys just before sacrifice showed that neither lesion had produced detectable abnormality in the one of these two areas remaining. Thus, it appears that both are necessary for two of the tests and that only "area 3" is necessary for the others. An exception to the above statement is that either or both areas (or indeed all of currently recognized somatosensory cortex of the hemisphere contralateral to the hand tested) can be ablated without producing any long-lasting impairment in fine temperature discrimination. Preliminary data indicates that areas of the ipsilateral hemisphere participate in this, and probably other, forms of sensibility.

Scientific Significance to Bio-Medical Research: These experiments obviously are not wholly in accord with current views of the function of the primary somatosensory cortical areas. An unexpected capacity for fine sensory discrimination remains after removal of these areas, a discovery which strongly suggests that the neural code operative in the lemniscal system (involving the narrowly-tuned, topographically-arranged neurons unique to this system) is not the only means by which the animal is able to achieve a high degree of accuracy in somesthetic perception. Apparently, there must be a different, but in some respects equally effective, code used by the extra-lemniscal system. Although little attention has been paid to this alternative way of conveying information, there are clues in the literature as to the principles by which it operates. The experiments described above are a first step in determining what each kind of code is peculiarly suited for. In a practical vein, our success in retraining monkeys with initial postoperative deficits, and the concomitance of their sensory recovery with the return of their motor competence, suggests that stroke patients might benefit more from retraining in sensation than from a program of therapy centered purely on motor abilities.

Proposed Course of Project: Many more carefully-designed behavioral tests will

be needed in order to determine in what ways the lemniscal and extra-lemniscal somatosensory systems are functionally different, as well as the ways in which their functions may overlap. We intend to utilize more complicated stimuli that heretofore in the "passive touch" situation in order to find out whether or not the operated animals' success in this situation can be ascribed to the simple kinds of stimuli used up to now. We also intend to make more extensive lesions than previously in the attempt to discover how impairment can be produced in temperature discriminations (performed in the "active touch" situation) and in those tasks so far successfully performed when only "passive touch" is employed.

Honors and Awards: 1. Membership, Experimental Psychology Study Section, DRG, 1969-1973.

2. Editorship, CORTEX, 1968- .

Publications:

Deuel, R.K., Mishkin, M., and Semmes, J.: Interaction between the hemispheres in unimanual somesthetic learning. Exptl. Neurol. 30: 123-138, 1971.

Schwartzman, R. J. and Semmes, J.: The sensory cortex and tactile sensitivity. Exptl. Neurol., 1971, in press.

Semmes, J.: Somesthetic effects of damage to the central nervous system. In Jung, R. (Ed.): Handbook of Sensory Physiology. New York, Springer-Verlag, in press.

Semmes, J.: Review of M. S. Gazzaniga, The Bisected Brain. Science 171, 885-886, 1971.

Serial No. M-P-CB-(c)-1
1. Laboratory of Psychology
2. Section on Comparative Behavior
3. NIH Animal Center, Poolesville, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Learning and Motivation in Relation to Behavioral Development

Previous Serial Number: Same

Principal Investigators: Walter C. Stanley and W. Edward Bacon

Other Investigators: E. Faye Bacon and Holly L. Neyman

Cooperating Units: None

Man Years

Total:	4.56
Professional:	1.55
Other:	3.01

Project Description:

Objectives: To understand adaptive and maladaptive behavioral organization in adults, it is necessary to: (1) systematize prior findings and conclusions into coherent and testable theoretical schema; and (2) study experimentally the possible relationships of early learning and motivation to behavioral development. Studies are needed on: the kinds and amounts of organization inherent in neonatal behavior; principles according to which early behavior may be reorganized, especially the role of learning in behavioral reorganization; and the relationships between early experience and later adult behavior and adjustment.

Methods Employed: The world scientific literature on early learning and motivation, particularly as it relates to behavioral development, is continually surveyed and related to the specific experimental and observational research findings of the Section. Data are collected, utilizing both free operant and discrete-trials instrumental conditioning procedures. The operant procedures focus on properties of neonatal key lifting, nipple latching, and sucking behavior; the instrumental procedures focus on properties of positive and negative stimuli controlling locomotory approach and avoidance behaviors. The study of motivational phenomena included procedures where milk was

directly injected into the stomach without passing into the mouth and where the effects of nipple structure on sucking could be systematically studied.

Subjects: In most experiments, subjects were purebred beagle dogs, 1 - 5 days of age when received in the laboratory. They were offspring from a purebred beagle colony maintained by Affiliated Medical Enterprises, Inc., at Princeton, N. J., under Contract No. PH 43-67-734, for the purpose of providing relatively homogeneous canine infants with known early histories for use by the Section on Comparative Behavior. The dog is the primary subject because of his social affinity to man, his existence in a variety of closely related genetic forms (breeds), the variety and complexity of his emotional responsiveness, and his relatively large size at birth which makes complex automated procedures and apparatus easier and cheaper to design, fabricate, and utilize in behavioral research.

Major Findings:

1. Orderliness and continuity of behavior in infancy. Neonatal dogs (that is, dogs less than two weeks of age) yielded orderly and typically linear curves of general bodily activity overnight when cumulative activity counts were plotted on half-hour periods of time. Every two minutes these subjects received short-term, mildly aversive air stream which they could postpone for two minutes by simply moving enough to produce one count on an activity meter. The linearity of the activity curves indicated that no special local behavioral processes supervened to alter the regular expression of overnight activity.

Sucking in neonatal dogs can persist for hours under some conditions. In a continuation of experiments on recycling progressive ratio schedule of milk contingent on sucking, an unusually persistent neonatal subject sucked for 2 and 1/2 hours without meeting the nonresponse criterion of 2 minutes of nonsucking. This unusual bout of long-term sucking was especially striking because during much of the latter part of the session the subject did not swallow milk that was injected into its mouth. Rather, the milk flowed out of its mouth as it continued to suck. The sucking displayed by this subject was comparable to the maximal sucking performance of acute physiological preparations tested by other investigators. They found that puppies whose stomachs had been anesthetized sometimes sucked for as long as 2 and 1/2 hours.

2. Experimental analysis of feeding sequence. Resilient water-filled nipples yielded higher rates of sucking than harder or lumpy tubing-filled nipples. However, this conclusion held only with subjects who were tested on all three types of nipples. Subjects who were tested only on one type of nipple throughout the experiment did not display sucking rates which differed other than by chance among the three nipples. Thus, within-subjects comparisons yielded systematic and statistically highly significant differences correlated with nipple structure, while between-subjects comparisons

yielded only chance differences. Further analysis of the findings indicated no evidence that some special behavioral process, as stimulus contrast, supervened in the within-subjects experimental design to account for the findings. Apparently, the success of the within-subjects design was due entirely to its exclusion of extraneous, uncontrolled variables which produced large differences in sucking. There was some suggestion that subjects randomly assigned to the water-filled nipple condition in the between-subjects design were poorer suckers. However, the superiority of the water-filled nipple in generating sucking was present in low- as well as high-sucking subjects assigned to the within design.

In a second series of experiments concluded this year, we examined the effect of 10-, 15-, 20-, and 25-mm. length nipples on nonnutritive sucking. The 15 mm. length was optimal with rate of sucking and amplitude of sucking tending to fall off when a length other than the 15 mm. nipple was used. Moderate vs. overnight food deprivation had no systematic effects on the sucking measures, showing that under some conditions external stimulus control of sucking is far more powerful than internal physiological state.

3. Experimental synthesis of behavior in operant conditioning situations. Last year we first devised and tested procedures for the study of operant key lifting in neonatal dogs, with milk as the reinforcement. This year we confirmed our findings that infant puppies will learn to lift the key with their noses throughout many sessions, even when as many as 9 or 10 key lifts are required to bring the nipple into the compartment only once. We also found that when milk is omitted, the key-lifting behavior extinguishes with or without continuation of nipple insertion. This means that nonnutritive sucking alone does not act as a reinforcer in the situation. Milk, however, is absolutely essential. When the same puppies have milk reintroduced in the situation, the effects of extinction are counteracted and key-lifting behavior is resumed at essentially the same rate it was occurring before milk was omitted.

The powerful effect of milk as a reinforcer suggested that the operant key-lifting situation would be an excellent one in which to study further the locus of milk reinforcement itself. Is mouth stimulation by milk alone necessary? Or, is stomach stimulation alone necessary? Or, does the reinforcing effect require both mouth and stomach stimulation by milk? We began the series of experiments with more than usual optimism because we had previously found that sucking behavior itself was markedly sensitive to direct intragastric milk injection. It appeared that milk entering the stomach while bypassing the mouth acted as a reasonably stable reinforcer when made contingent on sucking. Accordingly, we tried to train puppies to lift the key when key lifting was followed by direct intragastric injection of milk. The experiments were complete failures. The puppies not only did not learn the key lifting but became extremely lethargic. Instead of gaining behavior, the puppies seem to lose it.

We, therefore, simplified the task considerably, substituting for the key manipulandum a button which was placed in the nipple hole of the apparatus. Direct intragastric injection of milk was made contingent on button pushing. There was some suggestion that one or two subjects may have been conditioned, but the performances were highly unstable and not as sensitive to the omission of milk as we deem necessary for a convincing demonstration of learning.

Finally, we made the most sensitive test possible to determine if any reinforcing effect of intragastric milk injection had occurred. We first trained subjects to lift the key on the basis of intra-oral injection of milk which they could then swallow normally. After the subjects had learned the key-lifting response, we tested half of them by omitting milk but continuing to insert the now empty nipple. For the other half of the subjects, we omitted intra-oral injection of milk and substituted direct intragastric injection of milk. There was no evidence that the intragastric injection of milk retarded extinction of key lifting. Thus, when sucking (only one of the constituent elements of the feeding sequence) is studied, intragastric milk injection has an apparent reinforcing effect. However, when the puppy must "synthesize" divergent elements of the feeding sequence into a smoothly flowing adaptive behavioral pattern, intragastric milk injection fails utterly to do the job.

Our final exploitation of the method of experimental synthesis, using the key-lifting procedure, has to do with observations of sources of maladaptive behavior. After the key-lifting response was learned, some subjects showed a markedly aberrant pattern of behavior. This was a blocking of the key-lifting sequence by an undue prolongation of general bodily inactivity correlated with sucklike movements of the mouth. Examination of this prolonged maladaptive state indicates that it is usually correlated with the tongue being flattened and against the upper palate. We have labelled this response TOR (tongue-on-roof-of-mouth sucking). More rarely, the abnormality appears as a TOF (tongue-on-floor-of-mouth) sucking. In either case, the posture of the puppy is dominated by extension and general immobilization. The abnormality occurs during postreinforcement pausing, i.e., after retraction of the milk-containing nipple from the experimental space. The maladaptive pattern is absent during extinction when milk is omitted. This shows that the abnormality is not due to some kind of physiological or neurological deficit in the ordinary sense.

4. Stimulus control of instrumental crawling behavior in neonatal dogs. To determine whether the discriminated behavior of newborn puppies is under both excitatory and inhibitory control of discriminative stimuli, infant dogs were trained on a successive discrimination problem using either tactile or temperature cues. After stable performance was acquired, we either changed (generalization test), partially changed (combined-cue test), or reversed (resistance-to-reinforcement test) cues. Results indicated that the behavior

was under the excitatory control of the cue (S+) correlated with reinforcement but not the cue (S-) correlated with nonreinforcement. Puppies appear to respond to the presence of S+ and not to respond to the absence of S+ rather than the presence of S-. Further, we found that puppies acquired much more stable discriminated behavior and acquired the behavior more rapidly when tactile, as compared to temperature, cues were used.

5. Comparative studies of neonatal learning. Analysis of previously collected data on newborn kittens indicated that the relationship of escape responding to motivational level was similar to that found with adult mammals. However, the avoidance responding of infant cats was less stable and of a different form than that we obtained previously with infant puppies.

Significance: One assumption concerning behavior is that it is a "sometime" or episodic event, to be understood in terms of variables or vectors operative only during stimulus presentation or during trials in learning situations. An alternative point of view holds that behavior has larger organizational properties which transcend successive stimulus presentations and the mere succession of learning trials. Much of the data on neonatal behavior in dogs that we have collected and analyzed during the past year are consistent with the latter view. The neonatal dog, far from being a simple reflex animal, is not only a capable learner in a great variety of situations, as we concluded last year, but also an organism whose behavior may be integrated over many minutes and even hours of performance.

A second assumption is that brain myelinization in the developing mammal is closely correlated with learning ability. Because the brain of the puppy less than two weeks of age is relatively unmyelinated, our findings are contrary to this view.

In view of the greater complexity of the human infant, the present data on neonatal dogs suggest that we drop certain widely held simplistic views concerning behavior in neonates. Instead, we must recognize that neonatal behavior is highly similar to adult behavior in some respects, but also markedly different from adult behavior in other respects. Programs of research and correlated theory restricted either to similarities or to differences alone are incomplete approaches. Worse, they probably have misled more research and practical application than they have guided.

The neonatal mammal must ingest food to survive. It is, therefore, not surprising that its ingestive behavior and responses closely related to ingestive behavior should be dynamically so similar to what we find in the adult. Perhaps our most striking example of such dynamic similarity is our discovery that direct injection of milk into the stomach will not support previously learned operant key lifting -- even when such key lifting is followed by nipple insertion and sucking by the subject which, in turn, is followed by milk

being injected directly into the stomach. As we made this discovery, investigators working elsewhere on adult rats reported a similar discovery. The reinforcing action of direct injection of food into the stomach of the adult rat occurred only when correlated with stimulation of mouth and components of feeding behavior.

Conversely, studies on stimulus control seem more in line with the assumption of differences between adult and neonate. Other investigators have found that adult subjects, such as pigeons and rats, can be trained so that their responses to negative and positive cues in discrimination situations are roughly equivalent in strength. In general, we have not found this to be true with respect to tactile and temperature discrimination learning in the neonatal dog. Instead, our findings continue to be in line with the traditional view that inhibitory processes seem to be weak and unstable in the neonatal dog.

Proposed Course of the Project: This project will continue within the general guidelines set by the objectives.

Honors:

Dr. Walter C. Stanley elected:

1. Fellow, American Psychological Association, Division 3, Sept. 1970.

2. Friend, The Jackson Laboratory, Bar Harbor, Maine, Dec. 1970.

Invited Activities:

1. W. C. Stanley: Chairman, "Animal Conditioning" Section of Program, Psychonomic Society, 11th Annual Meeting, San Antonio, Texas, Nov. 1970.
2. W. E. Bacon: Colloquium, Nature of Learning in Newborn Mammals, Dept. of Psychiatry, McMaster University, Hamilton, Ontario, Aug. 1970.
3. W. C. Stanley: Research Reports, Third Symposium on Oral Sensation and Perception: The Mouth of the Infant, National Institutes of Health, Bethesda, Md., Nov. 1970:

    i. Perspectives in behavior organization and development resulting from studies of feeding behavior in infant dogs.

    ii. Blocking of feeding sequence correlated with prolonged maladaptive suck-like action in the puppy.

4. W. C. Stanley: Lecture, Learning and Motivation in Neonatal Dogs, at George Washington University, Department of Psychology, Wash., D. C., Dec. 1970.
5. W. C. Stanley: Lecture, Learning in Infancy, at University of North Carolina, Student Colloquium, Department of Psychology, Chapel Hill, N. C., Feb. 1971.
6. W. C. Stanley: Lecture, Learning in Infancy, at Johns Hopkins University, School of Hygiene and Public Health, Balto., Md., March 1971.

Permission granted to reprint article:

Stanley, W. C., Cornwell, A. C., Poggiani, C., and Trattner, A. Conditioning in the neonatal puppy. J. comp. physiol. Psychol., 56: 211-214, 1963.

i) in Biobehavioral Bases of Development, a college textbook by Victor H. Denenberg, to be published by Sinauer Associates, Inc., in 1971.

ii) in Sluckin, W. Readings in Early Learning and Early Experience, to be published Penguin Books.

Publications:

1. Clark, R. G., Milhorat, T. H., and Stanley, W. C.: Experimental pantopaque ventriculography. J. Neurosurgery, 34: 387-395, 1971.

2. Bacon, W. E., and Stanley, W. C.: Avoidance learning in neonatal dogs. J. comp. physiol. Psychol., 71: 453-458, 1970.

3. Bacon, W. E.: Stimulus control of discriminated behavior in neonatal dogs. J. comp. physiol. Psychol. In Press.

4. Stanley, W. C.: Perspectives in behavior organization and development resulting from studies of feeding behavior in infant dogs. In Bosma, J. F. (Ed.): Third Symposium on Oral Sensation and Perception. The Mouth of the Infant. Springfield, Ill., Charles C Thomas, Chapt. 7. In Press.

5. Stanley, W.C.: Blocking of feeding sequence correlated with prolonged maladaptive suck-like actions in the puppy. In Bosma, J. F. (Ed.): Third Symposium on Oral Sensation and Perception. The Mouth of the Infant. Springfield, Ill., Charles C Thomas, Chapt. 17. In Press.

Serial No. M-P-CB-(c)-2
1. Laboratory of Psychology
2. Section on Comparative Behavior
3. NIH Animal Center, Poolesville, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Development of Social and Emotional Behavior

Previous Serial Number: M-P-CB-(c)-2

Principal Investigators: Walter C. Stanley and W. Edward Bacon

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.20
Professional:	.10
Other:	.10

Project Description

Objectives: To survey the world scientific literature on sources of positive and negative attraction and reinforcement inherent in social contact, systematize relevant theoretical concepts, and conduct experiments, especially on nonhuman animals. The experimental aims are to: analyze the deprivational, emotional, and other factors responsible for the efficacy of the social reinforcers; and compare the action of social reinforcers and related variables with the action of homeostatic reinforcers, such as food for a hungry animal.

Methods Employed: Apparatus suitable for the study of the development of social and emotional behavior in juvenile and adult dogs was designed and placed on order for use in the new Biopsychology Building where the Section's research will henceforth be housed. In designing and constructing this new research apparatus, the following criteria were used: to avoid insofar as possible small cagelike enclosures and to substitute therefor larger pens and runways to make the behavior studied more naturalistic; to automate insofar as possible the natural feeding, watering, and caretaking of the juvenile and adult subjects to permit complete control over the subjects' contact with people; and to have apparatus available for the coming year whose purpose will be to study primarily changes in the social and emotional behavior of juvenile dogs as a consequence of differential contact and handling by human persons.

Major Findings: None during the current year as the data collection phase of the project was held completely in abeyance. But findings from the project, published in 1965, have been used by other investigators to challenge the notion that imprinting in infant animals is a special form of learning without reinforcement. Contact, it would seem, is the reinforcer. Studies are now needed to examine the role of different sense modalities in "contact" reinforcers.

Significance: Much human behavior in infancy and childhood is molded by the attention and response of adults toward both normal and pathological emotional attachments. The young dog's tendency to develop a strong emotional attachment to a handler provides a unique opportunity for the experimental analysis of the variables which may be responsible for such emotional attachments. The clear breed-correlated differences in dogs' speed of running to a person indicate that the dog is suitable for the study of the behavioral genetics of dependency and strong emotional attachments.

Proposed Course of the Project: To continue analyzing the results of experiments conducted while at another institution; prepare the analyzed data for publication; and begin collecting data and the measurement of social and emotional behavior as reflected in the speed of running, duration of contact, and rate of response emission of juvenile dogs in relation to persons as goal objects.

Honors and Awards: None

Publications: None

Serial No. M-P-CB-(c)-3
1. Laboratory of Psychology
2. Section on Comparative Behavior
3. NIH Animal Center, Poolesville, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Behavioral Mathematics and the Logic of Measurement

Previous Serial Number: Same

Principal Investigator: Walter C. Stanley

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.340
Professional:	.05
Other:	.290

Project Description:

Objectives: To develop a logic and mathematics directly relevant to the measurement of stable and changing behavior as it occurs in learning situations in order that amount of behavioral change may be validly compared from one response class to another in the same or different organisms.

Methods Employed: Most applications of mathematics to behavioral data represent empirical curve-fitting, statistical analyses, or models, the terms of which refer to inferred or assumed processes. The present effort differs from traditional approaches by starting from a theory of measurement rather than from a theory of behavior or learning. It also differs from traditional approaches by assuming that the relevant mathematics (number system and functions) must be abstracted, rather than inferred, from directly recorded and reinforced behavioral elements. Each behavioral element of a definable and recordable behavioral class is regarded as uniquely specifiable by the assignment of two numers, one symbolizing order of occurrence (c) of the behavioral elements, the other, time (t) of occurrence.

Major Findings: The major effort this year was to systematize and relate findings on this project to methods of data analysis as reported by Dr. Stanley

at the Third Symposium on Oral Sensation and Perception. The Mouth of the Infant, at the National Institutes of Health, Bethesda, Md. The rules for assigning numbers to behavior were clarified by showing that, in any situation, numbers must be assigned to behavior so that those assigned to reference response class ($\underline{c}$) plus those assigned to non-occurrence of response class ($\underline{c}'$) must always add to give the total amount of behavior ($\underline{b}$), i.e., $\underline{c} + \underline{c}' = \underline{b}$. Using time units for measurement, the temporal equation parallel to the above behavioral equation is: $\underline{t}_c + \underline{t}_{c'} = \underline{t}_b$, where $\underline{t}_c$ is time correlated with the occurrences of the reference response, $\underline{t}_{c'}$ is the time correlated with non-occurrences of the reference response, and $\underline{t}_b$ is total behavioral time equivalent via multiplication by an appropriate constant to ordinary physical time.

Significance: Work aimed at the induction of a behavioral number system and mathematics, it is believed, is propaedeutic to true measurement in the behavioral sciences.

Proposed Course of the Project: To continue working on the mathematics of behavior occurring in learning situations and to continue work in the development of a logic of behavioral measurement.

Honors and Awards: None

Publications: Incorporated into chapter entitled: Perspectives in behavior organization and development resulting from studies of feeding behavior in infant dogs. For reference, see M-P-CB-(c)-1, Page 7.

Serial No. M-P-CB-(c)-4
1. Laboratory of Psychology
2. Section on Comparative Behavior
3. NIH Animal Center, Poolesville, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Automated Apparatus for the Study of Animal Infant Behavior

Previous Serial Number: Same

Principal Investigator: Walter C. Stanley

Other Investigator: Stephen N. Lee

Cooperating Units: Technical Development Section, IR, NIMH

Man Years

Total:	.65
Professional:	.10
Other:	.55

Project Description

Objectives: To design, construct, and evaluate apparatus suitable for maintaining, at one time, at least four mammalian infants away from their natural mothers and for simultaneously permitting the scheduling, control, measurement, and machine plotting of sucking, key nosing, vocalization, and locomotory behavior.

Methods Employed: Infant dogs less than two weeks of age have been maintained for over two weeks in individual compartments placed on a turntable which automatically moved to a feeding station. The feeding station consisted of a nipple on a moving carriage and connections necessary for the recording of both negative pressure producing and the nipple manipulative components of sucking behavior and for the delivery of milk contingent on the suction component of sucking. The action of the apparatus and the behavior of the experimental subjects were observed around-the-clock to determine ways of improving the efficiency and consistency of operation of all elements of the apparatus and the ease with which puppies can feed themselves. A single-animal (one-compartment) apparatus has been built to pretest additional features to be incorporated in the carrousel.

Major Findings: Computer (LINC) programs were devised and found suitable for controlling two or more classes of discriminative stimulation in situations where the delivery of milk was programmed contingent on sucking by neonatal dogs, placed in the compartments of the multiple-unit (carrousel) apparatus. Programming and interfacing were worked out in relation to individual-unit apparatus so the LINC could control automatically two independent key-lift apparatuses, permitting: (1) two subjects to be run simultaneously, but independently, with same reinforcement schedule; and (2) two subjects to run simultaneously, but on different reinforcement schedules. A beginning was made on integrating the Section's incremental tape recorder with the calculating potential of the Section's LINC. Programs were also worked out for the plotting by computer of data collected in both instrumental and operant conditioning situations.

Significance: Perfection of this highly specialized apparatus will: i) reduce, but not eliminate, the need for around-the-clock personnel; ii) permit more than one experiment to be conducted simultaneously by the personnel available; iii) allow the research on canine infants to be extended to other mammals; and iv) permit physiological as well as behavioral study of neonatal mammals.

Proposed Course of the Project: Continuation of efforts until attainment of: i) full and true computerized programming of animal infants' maintenance and feeding; ii) reliable and valid objective recordings of their sucking, nipple latching, locomotory, vocalizing, and choice behavior; and iii) publication of description of apparatus, either as a separate article or as part of data article, in an appropriate scientific journal.

Honors and Awards: None

Publications: Incorporated into chapter entitled: Perspectives in Behavior Organization and Development Resulting from Studies of Feeding Behavior in Infant Dogs. For reference, see M-P-CB-(c)-1, Page 7.

Note: Physiological investigators at other institutions have requested and been sent descriptions of the multiple-unit apparatus.

Serial No. M-P-CB-(c)-5
1. Laboratory of Psychology
2. Section on Comparative Behavior
3. NIH Animal Center, Poolesville, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Intracranial Stimulation in the Neonate

Previous Serial Number: Same

Principal Investigator: W. Edward Bacon

Other Investigators: Ira G. Wong and Walter C. Stanley

Cooperating Unit: Section on Histopathology, Laboratory of Pathology, DBS

Man Years

Total:	.20
Professional:	.20
Other:	0

Project Description

Objectives: (1) to develop a method of behavioral control by stimulation of neural tissue that will be useful in the study of behavioral development; and (2) to determine the interrelationships of neural structure and behavior during early life and the degree of correspondence to adult structure-function relations.

Methods Employed: Electrodes were implanted into subcortical structures of neonatal dogs. Puppies received tactile preference tests in a two-compartment chamber where electrical brain stimulation was correlated with presence in the nonpreferred compartment and also received training trials in a T-maze where electrical stimulation was contingent upon a puppy's entry into the non-preferred arm.

Major Findings: Analysis of previously collected data indicates that the tactile preferences of infant dogs can be controlled by direct electrical stimulation of the brain. Changes in behavior occurred when brain stimulation was coincident with (preference tests) or contingent on (T-maze training) a particular response. The changes in behavior occurred only when brain structures corresponding to adult reward areas were stimulated.

Significance: (1) Electrical brain stimulation can modify the behavior of a very young organism and, thus, provide a useful technique for studying early behavioral organization. (2) Electrical brain stimulation modifies the behavior of the very young and the adult in much the same way, indicating that the phenomenon of intracranial self-stimulation has wide ontogenetic generality. (3) There is close correspondence in structure-function relationship between infant and adult despite differences in the details of brain structure. This suggests that interrelationships of neural structure and behavior also have ontogenetic generality.

Proposed Course of the Project: The first objective has been fulfilled and the second objective also has been met with a small sampling of structures. The project is terminated as an independent project. A research report has been prepared and submitted for publication.

Honors and Awards: none

Publications: none

Serial No. M-S-C-11
1. Socio-environmental Studies
2. Office of the Chief
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Social Psychological Correlates of Occupational Position

Previous Serial Number: Same

Principal Investigators: Melvin L. Kohn and Carmi Schooler

Other Investigators: Lindsley Williams (guest worker, on assignment from the Career Development Program in Global Community Health, HSMHA)

Cooperating Units: None

Man Years

Total:	5
Professional:	1½
Other:	3½

Project Description:

Objectives: To ascertain the relationship of some principal dimensions of job, occupation, and career to relevant aspects of men's values, social orientation, self-conception, and off-the-job behavior.

Methods Employed: Structured interviews with a sample of 3100 men, representative of all men employed in civilian occupations in the United States.

Major Findings: A. The social psychological impact of occupation.

In earlier years, sociologists wrote fascinating case studies of how particular occupations--railroading and teaching are two prime examples--mold the lives of those who work at them. As we have moved from broad-ranging descriptive accounts to more precise quantitative investigations, the focus has narrowed. To most sociologists, "occupation" has come to denote little more than occupational status--an important, but surely not the only important, facet of occupation. To some specialists, the relationship of occupation to personality has been reduced to the problem of fitting the man to the job. And to others, the problem has come to be limited to the effective performance of men in their jobs, or their subjective reactions to those jobs.

The study reported here represents a systematic effort to address the old problem, the effects of occupation on the man, with new statistical tools. As in the past, the problem is the far-ranging social psychological impact of occupation--on values, social orientation, self-conception, and intellectual functioning. In contrast to the early studies of particular occupations, though, the strategy now is to collect data about a broad range of occupations, based on a representative sample of all employed men. To be able to determine which aspects of occupation affect which aspects of social psychological functioning, we try to secure systematic data about all those dimensions of occupational experience we have any reason to believe to be pertinent.

Past annual reports have described our intensive examination of two facets of occupation, chosen because of their presumed theoretical importance: (1) the occupational conditions conducive to or deterrent of the exercise of self-direction in work, because we hypothesized these to be of central importance for understanding the psychological impact of social class; (2) bureaucracy, because of its prominence in sociological theory and because of the popular belief that its effects are both great and deleterious. In these analyses, other occupational dimensions served secondary roles, as intervening variables or as controls. Now we are looking more systematically at the entire range of occupational dimensions that we have indexed.

This year's principal accomplishment has been the assessment of the comparative potency of these many dimensions of occupation, and the classification of the more potent dimensions into theoretically meaningful clusters. Together, these clusters define the structural imperatives of the job: (1) its organizational locus [ownership, bureaucracy, position in the supervisory hierarchy]; (2) whether it facilitates or inhibits the exercise of occupational self-direction [closeness of supervision, routinization, substantive complexity]; (3) job pressures [time pressure, overtime, heaviness of the work, dirtiness]; and (4) uncertainties [the likelihood of a dramatic change in the man's situation, the frequency with which men in his position are held responsible for things outside of their control, the risk of loss of job or business]. These--independently of educational attainments, of each other, and of all of the other dimensions of occupation that we have measured--bear significantly on men's social psychological functioning.

By contrast, some facets of work that have been at the forefront of attention in occupational sociology prove to have little independent importance. Chief among these are occupational status and all those aspects of interpersonal relationship not directly involved in supervision or in the substantive complexity of the work. The potent occupational variables are not the extrinsic benefits that the job confers nor the interpersonal relationships

in which it is enmeshed, but the structural imperatives of locus, self-directedness, pressure, and uncertainty.

These analyses also show that the principal relationships of occupation to social psychological functioning are "reasonable"--they have face validity. Pressures and uncertainties, for example, bear more heavily on anxiety, while substantive complexity is more pertinent to intellectual functioning.

At this point, we still face many important analytic problems in establishing the direction of causal relationships. We have some evidence that men's reports about their jobs are not distorted by their own needs--for example, reports about time pressure are not much affected by how anxious the men are. We have also found that the relationships of occupation to social psychological functioning are not attributable to age, race, religion, or other background variables. But we have only begun to deal systematically with the questions of how much opportunity men have to mold their jobs, and how much real choice they have, with respect to each of the pivotal dimensions of occupation, in choosing and/or leaving jobs. Analyses are underway on all these issues, but a great deal remains to be done.

B. The 'fit' of individual and community characteristics.

Lindsley Williams is combining the social psychological data of this study with basic data about the principal communities in which the research was carried out, to see how the "fit" between individual and community characteristics affects social psychological functioning. The research is directed at several objectives. The first is to demonstrate that human values and orientations vary from one urban setting to another. The second seeks to understand these variations in terms of the differing social characteristics of the several communities. The third and most important objective is to explore individual variation in terms of the consonance or dissonance of the social context in which the individual finds himself.

The Occupations study data include information on the individual's social characteristics; among these are age, race, marital status, occupation, religious affiliation, nativity, education and an index of social class. These are central to the proposed analysis of social consonance or dissonance, which requires that individual and collective status be juxtaposed.

At this point, our data do not suffice and attention must shift to data published by the U. S. Bureau of the Census for urban and metropolitan areas (S.M.S.A.s). While the Census does not inquire (or tabulate) data which relate to all those social characteristics listed above, they do provide information, by race and sex,

on the distribution of age, education, income and occupation in the community and, to a lesser extent, in tracts and other small tabulating areas; the proposed investigation would concentrate at the community level.

Utilization of Census information has some distinct advantages. Not only is much of it based on the population instead of samples, the data are also independent from the data about individuals. This responds effectively to some of the criticisms that have been directed at the contextual analyses in which data about both individual and collective characteristics derive from reports by the same individuals.

The inquiry is being carried out in several steps. The first will be an intended confirmation that human values and social orientations do vary from one community to the next. The second step will be an examination of the social characteristics of the communities in the sample. Here the logic is to restructure the community data in order to permit treatment in meaningful social categories instead of referring to specific communities. Thus, the analysis would shift from the "nominal" level to a more general one.

At the conclusion of this step, it becomes possible to begin the analysis of variance in terms of community social characteristics, that is, community qua community. Here it becomes possible to perform analyses along dimensions such as population and density, and within realms such as occupational structure, educational distribution, and racial context. Since this analysis is especially concerned with social composition, some attention will be given to the profile of the community as well as its mean or median level. Consider occupational distribution, for example. If examined with an eye to national distribution, any single community could be characterized along a continuum from highly homogeneous to highly heterogeneous; similarly, it could be characterized with respect to pronounced voids and excesses: compared to the rest of the country, Washington, D. C. has a disproportionate number of bureaucrats. Thus, both central tendency and profile will be examined.

The last stage of the analysis will be an examination and interpretation of the relationship between individual and community social characteristics. This relates the individual not only to the community as a whole (his education versus that of the community at large), but indicates whether he is isolated or socially distinctive from the mainstream (one of the few Ph. D.'s in St. Louis or a Chinese in Atlanta). Here again, features of the sample become relevant: since the data derive from employed men, the data will be unable to speak to many of those with extreme problems: for example, the unemployed, especially those perpetually in this status. While this may be a weakness, it seems reasonable to expect that any relationship involving socio-contextual dissonance and consonance would only intensify as individual social characteristics become more varied.

Scientific Significance: In industrial society, occupational role is of central importance in shaping men's conceptions of self and of social reality. This research is addressed to a systematic appraisal of precisely which aspects of occupation affect which facets of man's social psychological functioning.

Proposed Course of Project: The analyses on which we are now embarked will continue indefinitely: the data are rich and the scientific payoff has thus far been considerable, but the analytic problems are exceedingly difficult and it would be foolhardy to expect them to be solved quickly.

Honors and Awards: None

Publications:

Kohn, M. L.: Bureaucratic man: a portrait and an interpretation. American Sociological Review, in press.

Kohn, M. L.: Class, family, and schizophrenia: a reformulation. Social Forces, in press.

Serial No. M-S-D-10
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Research on the Processes of Internalization of Rules, Standards, and Values

Previous Serial Number: Same

Principal Investigator: Roger V. Burton

Other Investigators: None

Cooperating Units: None

Man Years

Total:	5/6
Professional:	5/12
Other:	5/12

Project Description:

Objectives: This project entails research on conditions leading to self-control in a cheating situation. One objective in this program was to investigate the relations between measures of behavior during temptation and of fantasy involving deviation.

Another facet of this project is to investigate the child-rearing practices characteristic of parents whose children cheat or abide by rules in the cheating test. Previous investigations have tended to obtain measures of child rearing through interviews and questionnaires with the parents. The difficulties in interpreting such measures have been noted (cf. Project M-S-D-18, annual report for 1969-70). For the present study an attempt was made to obtain mother-child interactions in the test situation through direct observations.

A resistance-to-temptation test in a natural setting is a highly complex situation. Though certain factors may be experimentally varied to produce reliable differences in behavior for such situations, explanations of the results often require speculative assumptions about the motives that were involved in individual performance. Another objective of this project has been to assess the different motives that are aroused in cheating tests.

In the course of this research and the work of Project M-S-D-18, certain methodological issues of design, analysis, presentation of scientific reports, and the relation between this work and other published research have arisen. These considerations have led to fuller treatments of the immediate problems showing their relation to behavioral research in general.

Methods Employed: The measure of cheating is obtained by observations of an individual child's performance on a bean bag game. Deviation from the simple rules of the game are necessary to achieve a good score.

Stories using dolls to portray a deviation appropriate to a preschooler (aggression, irresponsibility with baby, damage to family property, etc.) were used to elicit the child's perception of a resolution to a conflict involving a behavioral standard. A before-after design permitted several analyses: predictions of cheaters and non-cheaters from the projective responses, discrimination of the two groups on the basis of the projective data immediately following the temptation test, and changes in their fantasy due to the arousal of the temptation. The same before-after design was used to study other motives that might be aroused in this particular test situation: level of aspiration, achievement, affiliation, and delay of gratification.

In the study of mother-child interaction in a temptation situation, all children were first tested alone. A week later, their mothers were asked to be with them while they were retested. The interactions were scored by direct observation from behind one-way mirrors. Immediately following the test, each mother was interviewed to explain fully the purposes of the study and to obtain information on the following areas: her notions of what the study was about and what we were measuring, and her judgment of how "normal" her behavior was during the test compared to her behavior at home, especially on the major dimensions we were scoring.

Major Findings: The findings for the study of fantasy projection using the doll-play stories were reported in detail last year. The additional analyses obtained this year involved control measures and showed no effect on the previously reported findings.

Analyses of the motivational measures of achievement, affiliation, aspiration, and delay of gratification are in progress, and there are not yet any reliable findings to report.

The data on the mother-child interactions in the temptation situation are also being analyzed. Though it is too early to report what the final picture of the analyses will show, some fascinating phenomena were observed. First, in spite of an attempt to reinforce

obedience to the rules of the game at the end of the first cheating test in all children, 95% of the children (19 out of 20) tested a second time under identical conditions behaved the same as they had a week earlier. By contrast, of the 60 children whose mothers were with them during the second temptation test, 38% changed in their behavior: 15% from cheaters to noncheaters and 23% became cheaters who had not cheated when by themselves. Thus it appears that a sizable proportion of the children who had internalized the self-control leading to resistance to cheating were influenced to cheat by their mother's presence. Preliminary analyses suggest the tentative interpretation that both a high conscience and high need to achieve are imbedded in the Puritan ethic of independence and self-reliance. The temptation test places these two motives of obedience to rules and high achievement in conflict. For some of these children, obedience to the rules was given priority when tested alone. When their mothers were present, achievement became more salient and led to breaking of the rules. In some cases the mother actually instructed her child to ignore the rules in order to achieve a good score in the game, even after the child told her that to do so was in clear violation of the rules that he was supposed to be following.

For the methodological papers, one issue deals with the use and misuse of partial and multiple correlations. In addition to consideration of the problem from our own analyses, the immediate stimulus was a report by Brewer, Campbell, and Crano (Sociometry, March, 1970). It was shown that the results of their analyses of specially generated data were completely derivable from well-known formulas and readily accessible tables, and that much smaller samples than they had used would still reveal artifactually significant relations. The purpose of the demonstration was to strengthen the relevance of the issues addressed by the authors. Furthermore, it seemed worthwhile to cite a few references to indicate to the general reader that these issues are currently very much alive in the statistical literature.

Consideration of another methodological issue was elicited by a paper dealing with reports of childcare attitudes, for which the respondents were mothers and grandmothers who were interviewed at the same point time. It was noted that a suggestion in the report that differences in attitudes between the generations reflected changes in childcare practices over time--an interpretation that unfortunately has many previous precedents--was unwarranted and misleading. Citations of findings from our analyses of retrospective data (Project M-S-D-18) demonstrated the untenability of such interpretations.

A request from the editor of Child Development to share thoughts of standards for published presentations of empirical research led to a paper published as an editorial for the journal.

The issues addressed included style of presentation, the need for a choice of indices for basic standards of reliability, validity, and magnitude and significance of relationships in the data, and the need for editorial consultants to have access to complete and clear descriptions of experimental, design, and analytical procedures in order to review a paper adequately, even if such material is only briefly noted in the published version.

Scientific Significance: These studies will contribute to an understanding of the socialization process, particularly to the inculcation of moral standards involved during temptation to cheat in an achievement situation. This information will add important empirical data necessary to the building of a comprehensive theory of socialization and of the development of conscience.

Proposed Course of Project: Analyses will continue on the above studies.

Honors and Awards: None

Publications:

Burton, R. V.: Correspondence between behavioral and doll play measures of conscience. Developmental Psychology, in press.

Burton, R. V.: On the misuse of partial correlations in hypothesis-testing research. Sociometry, in press.

Burton, R. V.: Standards for published presentations of empirical research. Child Development, in press.

Serial No. M-S-D-12
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Household Structure Related to Personality Development

Previous Serial Number: Same

Principal Investigator: Roger V. Burton

Other Investigators: None

Cooperating Units: None

Man Years

Total:	3/4
Professional:	5/12
Other:	1/3

Project Description:

Objectives: A previous paper in collaboration with John W. M. Whiting proposed a theory of sex identification called the status-envy hypothesis. The hypothesis is that a person identifies with someone who controls important resources. Such control requires at least the occasional withholding of a resource. The main research for that paper was a cross-cultural survey of primitive societies investigating the antecedent conditions for adolescent initiation ceremonies.

It was found that traumatic initiation rites were characteristic of societies in which the child had exclusive possession of the mother, i.e. the father slept elsewhere, during the child's first two years and also in which men had primary control of adult resources as indexed by patrilocality. Couvade occurred when both initial and later control was by women. The interpretation was suggested that the early control of the child by women produced an initial feminine identity. Later control by men produced a secondary masculine identity in conflict with the primary feminine identity. The initiation rite served to consolidate the boy's masculine identity. By contrast, the couvade is a society's way of permitting a man to act out his desire to be feminine.

We also attempted to show how the theory could account for findings from other types of research on identification that involved the father's role in the family, essentially comparing families with the father present or absent. Several testable hypotheses were suggested for future studies. The present study is an attempt to test some specific hypotheses derived from that theory.

Methods Employed: The society chosen for the study was Barbados since it was known to have a high proportion of father-absent households (the major antecedent dimension) and such household structure is not stigmatized, even when children are produced, as it might be in the continental United States. The children in the study attended a Roman Catholic elementary school, were primarily black, from lower-class families, and ranged in age from eight to fifteen.

The antecedent measures of household structure and background information were supplied by the headmistress and the teaching staff who have known these children and their families over many years (one nun having been in the school 30 years). The measures of sex identity were obtained from the Draw-A-Person (DAP) test.

Major Findings: The specific hypotheses derived from our theory were that degree of father presence as measured by household structure (father-present or father-absent household) would be positively related for boys to sex of first drawing and to differential size of drawings. All predictions received support in that by comparison to father-absent boys, boys whose fathers were continuously present were more likely to draw a male figure first, to draw male figures larger, and to draw their male figures larger than their female figures. In fact, all other groups drew females larger than they drew male figures. These findings were considered to add support to the theory of sex-identity based on status-envy.

Alternative explanations based on availability of male role models were not supported consistently. The measure of years of father's presence (and the highly correlated measure [r = -.98] of years of father's absence) was unrelated to sex of first drawing but did show significant associations with size of male drawing and difference in size of male and female drawings, though the magnitudes of the relations were less than those with the household measure of father absence. Measures of number of adult males living in the household (who might have served as adult male models or surrogate father figures) and of number of older male siblings showed no notable relations to any of the indexes of sex-identity.

Although predictions were based on the hypothesis that boys with absent fathers during their first two years would have conflict over sex identity, the evidence suggests that some of the father-absent boys may have both primary and secondary feminine identities.

Consideration of the extent to which adult males control resources in the Black Carib would support this idea. In addition, recent studies of the occurrence of couvade with individual men strongly indicate this possibility.

Comparisons of the effect of father absence during the first two years--a discrete, delimited measure of when absence occurred--and of the continuous, cumulative measures of number of years of absence or presence provided some tentative support for a critical period effect: it appears that feminine identity is more likely to occur if the father is absent during the first two years than if the absence occurs at later ages, even when the absence is for longer periods.

Controlling on age, ordinal position, achievement in school, and sex, age, and number of siblings did not affect these findings.

Scientific Significance: This research is relevant both for the evidence it provides regarding the impact of father absence on sex identity and for contributing to the formulation of a comprehensive theory of identification.

Proposed Course of Project: A paper has been prepared and submitted to a scientific journal.

Serial No. M-S-D-16
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Occupational Experiences of Musicians

Previous Serial Number: Same

Principal Investigator: Roger V. Burton

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: This study explores how adult coping mechanisms and personality measures determine and, in turn, are modified by reactions to naturally occurring stress in the occupational sphere of a group of highly competent, intensively trained persons who were strongly dedicated and committed to their professions. The sample is a select group of professional musicians, most of whom had been under contract to a motion picture studio. These men, whom this investigator had previously studied while under contract and when there was no indication of the future stress, suddenly became part of the large number of "free-lance" musicians competing for the diminishing demands for their skills. The precipitating event was the termination of all musicians' contracts in all studios.

Methods Employed: The main instrument in the earlier study had been the Guilford-Zimmerman Temperament Scale, a standardized, objective personality inventory. This test is again being used in order to have objective measures of changes which might have occurred since the loss of definite steady employment. Two other objective instruments are used--Rosenberg's Self-Esteem and Faith-in-People Scales--together with a semi-structured interview for information on the musician's background, musical training, reactions to the loss of a contract, and his current overall circumstances.

Major Findings: This project has continued to be inactive this year because of other commitments. Broadly speaking, the findings already cited for previous reports indicate that the large majority of these successful musicians have stable and desirable personalities. Furthermore, the increased pressure from decreasing work appears to have eliminated those with unstable characteristics and to have changed those who coped well toward being more competitive and indifferent about the plight of their colleagues.

Scientific Significance: Capitalizing on a previous study of these musicians, this project uses an unfortunate but naturally occurring event (contract termination) to investigate reactions to occupational stress. Stability of personality, predictability of individual ability to cope with occupational stress, and modification of personality through adaptation to major problems in life are some of the issues considered in this investigation.

Proposed Course of Project: Some analyses have already been performed though many still need to be done.

Honors and Awards: None

Publications: None

Serial No. M-S-D-23
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Observational Learning from Nurturant and Nonnurturant Models

Previous Serial Number: Same

Principal Investigators: Marian R. Yarrow, Phyllis M. Scott, and Carolyn Z. Waxler

Cooperating Units: None

Man Years

Total:	2
Professional:	1
Other:	1

Project Description:

Objectives: Can nurturance toward others be developed in young children through modeling and reinforcement procedures: How does the adult model's nurturant or nonnurant relationship with the child influence the child's learning?

Methods Employed: Conditions of high and low adult nurturance were developed in small play groups of nursery school children. Nurturance was provided by being friendly, showing attentive interest, giving affection, help, and encouragement. Low nurturance was critical aloofness. In these contrasting contexts, the adults performed a variety of standard responses. They also carried out modeling and reinforcement procedures intended to sensitize children to the feelings and plight of a victim in distress and to teach them not to remain passive in circumstances in which their actions could aid the victim.

Two culturally different samples of children were the subjects: inner-city day care children and children from upper-middle class suburbia. The children's experiences in the experiment covered a period of about eight weeks: Baseline testing, building a relationship with the experimenter, training procedures, and early and delayed testing. There was also a six-month follow-up. Observational

records and test protocols comprise the data. Observing and coding reliabilities range from r's of .81 to .98, and percents of agreement of 63 to 95.

Major Findings: The findings have been reported in detail in previous annual reports (1968 and 1969). They have been organized as two reports. One focuses on the influences of adult nurturant characteristics on the amount and content of what the child imitates, and on the degree to which the imitated behaviors are internalized and generalized. The second report is on the development of children's considerate and aiding responses when confronted with a victim in distress.

Scientific Significance: The effects of parental warmth and hostility have been of persistent concern in socialization research. Much of the theory dealing with nurturance effects, particularly identification theory, is based on naturalistic and clinical information. There are relatively few investigations of nurturance in which the variable is systematically defined and manipulated and its effects measured in terms relevant to the theories.

This study provides experimental evidence on the role of nurturance in the learning of a wide variety of kinds of behaviors. Further, only recently have investigators been concerned with the development of moral behavior in the sense of positive "conscience," rather than resistance to deviating conduct. This study is a step in the direction of understanding the origins of altruistic behaviors, particularly concern for the welfare of others.

Proposed Course of Project: The first report has been completed and has been submitted for publication. The second, a much longer document, is still in preparation. It is a report of the experiment in attempting to develop helpful and sympathetic behavior in the children. It includes, also, a critique and analysis of published work in altruistic behavior.

Honors and Awards: None

Publications: None

Serial No. M-S-D-26
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: An Observational Study of Maternal Models

Previous Serial Number: Same

Principal Investigators: Marian R. Yarrow and Carolyn Z. Waxler

Other Investigators: None

Cooperating Units: National Institute of Child Health and Human Development

Man Years

Total:	3/4
Professional:	0
Other:	3/4

Project Description:

Objectives: To describe patterns of maternal behavior that influence imitative responding in the very young child, and to examine these naturally occurring interactions in relation to theoretical formulations regarding the origins of imitation.

Methods Employed: Mother and child were observed together in a series of planned settings which permitted natural variations in kind and amount of mother-child contacts. The subjects were 36 Black mothers and their 20-month-old children, from lower and lower-middle economic groups in Washington, D. C. Contexts of interactions were a brief waiting period, play with standard toys, instructions to the mother to interest her child in new toys, instructions to the mother to get her child to imitate her behavior with a stuffed animal toy, and a mother surrogate's repetition of the mother's modeling. At another time, items from the Bayley Development Test were administered.

With the mothers' knowledge, interactions were observed and recorded from behind a one-way vision screen. Observer reliabilities range from 68% to 78% on exact matching of sequential behavior units.

Major Findings: The analyses have not been completed. Codings of just the mothers' behaviors point up differences in the skills with which mothers create and use opportunities for the child to learn through imitation; also there are apparent differences in the sensitivities with which mothers adapt their approaches to the child's state and with which they give appropriate and timely reinforcements. These differences will be examined in relation to child behavior.

Scientific Significance: Information regarding imitation in very young children is relevant to theories concerned with the origins of imitation. To date there is a paucity of systematic observational data on imitative learning in the second year of the child's life when, it is assumed, much learning occurs. Observations of mothers and children, particularly at a time when imitation is just beginning in the child's life, could provide a test of the formulations suggested by laboratory work with older preschool children of middle-class white backgrounds; it could also identify additional variables important in imitative learning.

Proposed Course of Project: A very small amount of staff time has been devoted to this project this year because of commitments on other projects. There will be continued work on data analysis in the coming year.

Honors and Awards: None

Publications: None

Serial No. M-S-D-27
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Child Effects on Adult Behavior

Previous Serial Number: None

Principal Investigators: Marian Radke Yarrow and Carolyn Z. Waxler

Other Investigators: Phyllis M. Scott

Cooperating Units: None

Man Years

Total:	2 1/4
Professional:	1
Other:	1 1/4

Project Description:

Objectives: Theories of socialization deal almost exclusively with the effects of adult behavior upon the child. It is customary to interpret differences in child behavior in terms of differences in parental treatment. This formulation fails to consider possible child influences on the caretaker and the interaction of both adult and child characteristics upon each other. The present study is addressed to the issue of child effects--how attributes of young children influence the behavior of their caretakers. Young children were observed in interaction with adults whose caretaking behavior had been programmed to be either nurturant or nonnurturant. To what extent, and in what systematic respects did child characteristics modify the adults' prescribed and intended caretaking?

Methods Employed: Two female adults were trained to be high and low nurturant caretakers for small groups of preschool age children. Interest, praise, help, affection, and respectful control defined nurturant caretaking. Withholding these behaviors, showing minimal attentiveness, using critical evaluation and arbitrary control characterized nonnurturance. Ethical considerations carefully set limits on adult behavior. Each adult performed both roles with different groups of children. Within a given role, the adult was expected to give similar treatment to all children.

One hundred eighteen upper-middle class children were observed in groups; nine groups had a nurturant caretaker; nine, a nonnurturant one. The adults were with the children for four half-hour play periods, spaced over two weeks.

Interactions were recorded in the form of dictated sequential accounts. Adult behavior was coded in the (above) categories of nurturance and nonnurturance. Child behavior with regard to the adult was categorized as seeking help, seeking approval, "clowning," attentiveness to adult, resistance, and inattentiveness. Interaction with peers was coded as friendly, aggressive, or neutral. Observer reliabilities ranged from 63% to 96%.

Major Findings: (1) Adult behavior with individual children varied greatly within each of the experimentally prescribed nurturance conditions, even though adult handling of each group of children was consistent with the prescribed high or low nurturant role. Variation in the frequency of direct bids for attention from different children led, by definition, to differences in adult responding. Dependent, attention-seeking children were successful in claiming more than their share of nurturance from these high nurturant adults. With a nonnurturant adult, dependent children, by creating more confrontations, fashioned for themselves caretakers who were more frequently rejecting. Although the experimental controls over adult behavior in this study limit generalization concerning these relations, the findings pose interesting questions: Do children's dependent qualities intensify nurturance from the warm parent or parent surrogate, and similarly do they magnify nonnurturance from cold parental figures?

(2) Many contacts with the children were initiated by the adult, not in response to a direct child overture. These provide the best index of child influences. The adult could have equalized her behavior toward all the children by initiating more contacts with children who had claimed less in direct overtures for attention, and by initiating fewer contacts with those who had drawn out a high rate of contact through their frequent bids. This did not occur. In fact, positive correlations between the frequency of adult responses to children's bids for attention and the frequency of initiated contacts are resounding evidence contrary to an expectation of general compensatory behavior by the adult:

(a) The low nurturant adult appeared to be significantly influenced by children's dependent behaviors. Children who were already receiving many rebuffs by virtue of their persistent attention-seeking were also taking the brunt of the adult's initiated nonnurturance ($r = +.44$).

(b) With the high nurturant adults, children's variations in dependency were not related to the adults' initiated nurturance. However, boys who sought help frequently and boys who resorted to clowning for attention received significantly more than their share of the nurturant adult's nonnurturance ($r = +.46$ for help-seeking and $+.88$ for clowning).

(3) Child characteristics in relation to peers made a difference in the nurturant adult's actions, but only in her negative approaches to children. High peer involvement (both aggressive and friendly), particularly by boys, was associated with more nonnurturance from the nurturant adult. Child characteristics in relation to peers were unrelated to variations in the nonnurturant adults' behavior.

(4) Boys' characteristics had generally stronger modifying effects on adult behavior than girls' characteristics. Also, boys tended to elicit more punitive adult responses than girls. Criticisms, the most explicitly punitive response, were given more often to boys than to girls by the low nurturant adult.

(5) Thus far we have reported child characteristics that increased nonnurturant behavior in both the nonnurturant and nurturant adults. To investigate a possible source of the nurturant adults' positive variability, child behavior was evaluated in terms of its reinforcing value for the adult. The following sequence was investigated: each of the adult's initiated positive contacts, the child's immediately following response, and the adult's subsequent initiated contact with the child. In this analysis we have retained the reinforcement formulation and reversed the characters in the plot: The child is the reinforcing agent; the adult is the subject of modification. Positive reinforcement of the adult by the child (interest, appreciation, affection) was effective in bringing the adult back quickly with another initiated positive contact, and nonreinforcement from the child resulted in much slower return by the adult. The adult was sensitive to this aspect of child responding--which seems to be a close parallel to the often demonstrated sensitivity of the child to adult positive reinforcement.

(6) The specific relations between child attributes and adult behaviors reported for the total sample were basically replicated when data on each experimenter were analyzed separately.

(7) Two research strategies were used in evaluating child effects on the adult. One related child traits to adult variations; the other analyzed specific sequences of child-adult behavior. The two strategies used together sometimes led to different interpretation than if either had been used alone. This is illustrated in the effects of children's clowning behavior. In the sequence

analysis, it appeared that the nurturant adults were relatively accepting of clowning. They gave positive attention to clowning bids 45% of the time; ignored them 30% of the time; and disciplined in only 25% of the occurrences. A quite different conclusion is reached from the trait analysis which asked how clowning-type children fared generally with regard to treatment from the adults. Clowning boys were unduly singled out for negative attention at times when they were not clowning. These findings illustrate how the adult's behavior toward the child is governed not solely by the child's immediate actions, but also by the images and expectations that the adult develops about the child.

Scientific Significance: In the present data, child effects on the adult were readily detectable. This has implications regarding theories of socialization. (Their present view of the child as molded by the adult is an incomplete formulation.) The challenge theoretically and methodologically is to examine the influence of both adult and child and to account for the cumulative interactive effects.

Proposed Course of Project: A report has been completed and is in press.

Honors and Awards: None

Publications:

Yarrow, M. R., Waxler, C. Z., and Scott, P. M.: Child effects on adult behavior. Developmental Psychology, in press.

Serial No. M-S-D-28
1. Socio-environmental Studies
2. Developmental Psychology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: An Inexpensive and Portable Means for One-Way Observation

Previous Serial Number: None

Principal Investigator: Roger V. Burton

Other Investigators: None

Cooperating Units: None

Man Years

Total:	2/12
Professional:	1/12
Other:	1/12

Project Description:

Objectives: Most research involving unobtrusive observational recordings employs one-way mirrors permanently installed as a part of a fixed laboratory setting or as a fixture in the portable laboratories built into trailers. Such installations have many desirable features but also some drawbacks, not the least of which is expense. The apparatus developed in this project is both inexpensive and permits greater flexibility than the permanent installations, an important consideration when designing behavioral studies in natural settings.

Method Employed: The design of the apparatus attempted to keep the cost to a minimum to allow for maximum convenience and flexibility when used for observations as well as when in storage, to contribute to ease of transportation and installation, and to soundproof the observational area as much as possible.

Scientific Significance: This apparatus may permit certain studies to be done that might not otherwise be carried out because of limited budget or because of the inability to observe in a given natural setting. It seems to have special applicability in university departments with large numbers of graduate students and limited numbers of facilities with permanently installed one-way mirrors.

Proposed Course of Project: Project completed.

Honors and Awards: None

Publications:

Burton, R. V.: An inexpensive and portable means for one-way observation. Child Development, in press.

Serial No. M-S-P(C)-23
1. Socio-environmental Studies
2. Personality and Environment
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Cultural and Psychodynamic Factors in the Occurrence and Treatment of Psychiatric Illnesses in Japan, Taiwan, and the United States

Previous Serial Number: Same

Principal Investigator: William Caudill

Other Investigators: Carmi Schooler, Hsien Rin

Cooperating Units: Department of Psychiatry, National Taiwan University, Taipei, Taiwan

Man Years

Total:	1
Professional:	1/2
Other:	1/2

Project Description:

Objectives: (1) To identify and describe the types and symptom patterns of psychiatric illnesses in Japan and Taiwan. (2) To determine the relationship of these types of illnesses to social, cultural, and psychological variables in Japanese and Chinese cultures. (3) To compare the results obtained with results from similar data on psychiatric patients in the United States.

Methods Employed: Methods have been described in detail in previous annual reports. Currently we are working with two samples obtained by use of the same schedule in interviews with patients and their families: (1) all admissions to five psychiatric hospitals in Tokyo during a twelve-month period in 1963-64 for a total of 994 patients; (2) all admissions to three psychiatric hospitals in Taipei during a two-year period, 1967-68, for a total of 1,009 patients.

The major task of coding these data has been completed during the current year. The Japanese data were coded in Bethesda, and the Taiwanese data in Taipei under the direction of Dr. Hsien Rin. Due to the present acute shortage of governmental funds for carrying

out research across national boundaries, it was fortunate that Dr. Rin could work directly with us for a week in Bethesda in September 1970, on his way back to Taipei from a conference sponsored by the Wenner-Gren Foundation for Anthropological Research.

Major Findings: We are at the beginning of the comparative analysis of the Japanese and Taiwanese data. Because we finished coding the Taiwanese data first, we began our analysis with those data. Using all Taiwanese patients between 15-60 years of age (890 patients, 396 males and 494 females), we carried out a series of factor analyses over the 33 most commonly occurring symptoms (each of which occurred in at least 8 per cent of the population) in order to determine the clearest patterning of the symptoms into a limited number of clusters. We did analyses separately for each sex, and also for the total patient sample. The clearest patterning of symptoms resulted in a structure of 7 factors for males, 5 factors for females, and 8 factors for the total patient sample. The three structures, however, are very similar, and we will indicate the nature of our findings to this point by briefly describing the 8 factor structure for the total sample.

The names we have given to the factors in the total patient sample indicate fairly clearly the types of symptoms underlying them: (1) blunted affect, (2) hostile behavior, (3) reality break, (4) depressed, (5) agitated, (6) headaches, (7) chronic fatigue, and (8) paranoid delusions. In contrast with previous analyses of Japanese patients from other samples, what seems surprising among the Taiwanese patients is the great amount of hostility and suspicion directed outward toward other persons, and the lack of phobic, tense, anxious feelings and behavior directed inward toward oneself. This latter tendency is especially prominent among Japanese patients. Thus, Taiwanese and Japanese patients seem to share certain probably universal clusters of symptoms such as a break with reality or depression, but the two groups also differ sharply in other regards.

We expect that the relative occurrence and intensity of the eight Taiwanese symptom factors will vary along such dimensions as sex, age, birth order, social class, and ethnic background (mainland Chinese versus native Taiwanese), and our next task is to explore the data along these dimensions. We will then do a similar set of analyses of the Japanese data, and then make comparisons between the Taiwanese and Japanese patients using matched sub-samples from the two countries.

A crucial question for us, beyond the present data, is to what degree do symptoms of hospitalized patients reflect the nature of emotional problems found in the general community? To help answer this question we are exploring the possibility of collecting such data from representative samples of people living in Tokyo and Taipei.

This further research hopefully will be carried out in collaboration with our colleagues in Japan and Taiwan, and Schooler will be working, in part, along these lines during his stay in Japan under a research award from the Japanese government from May through November 1971.

Scientific Significance: These studies will help to determine the extent and nature of social and cultural influences on types of psychiatric illnesses and their treatment. Past research has already shown the importance of these influences: although the general range of psychiatric illness is similar in various countries, there are also many differences that alter the pattern and course of the illness in terms of the cultural way of life and social position of the patient. If we are to understand these differences, and if we are accurately to determine what the basic and universal attributes of an illness are, then we must carry out cross-national and cross-cultural studies.

Proposed Course of Project: Analysis of the data will be continued using factor scores as the dependent variables and a series of biological, social and cultural characteristics of patients as the independent variables. In addition we plan to explore the possibility of obtaining data on the symptoms and problems of representative samples of persons living in urban environments in Japan and Taiwan.

Honors and Awards: Dr. Carmi Schooler has been awarded a Japanese Government Research Award for Foreign Specialists. This award is sponsored by the Japanese National Institute of Mental Health, and will permit Dr. Schooler to carry out research in Japan during the period May 1, 1971 to November 30, 1971.

Publications:

Draguns, J. G., Phillips, L., Broverman, I. K., and Caudill, W.: Social competence and psychiatric symptomatology in Japan: a cross-cultural extension of earlier American findings. Journal of Abnormal Psychology, 75: 68-72, 1970.

Draguns, J. G., Phillips, L., Broverman, I. K., Caudill, W., and Nishimae, S.: Symptomatology of hospitalized psychiatric patients in Japan and in the United States: a study of cultural differences. Journal of Nervous and Mental Disease, 152: 3-16, 1971.

Schooler, C.: Birth order effects: not here, not now! Psychological Bulletin, in press.

Serial No. M-S-P(C)-27
1. Socio-environmental Studies
2. Personality and Environment
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Parental Care and Child Behavior in Japan and the United States

Previous Serial Number: Same

Principal Investigator: William Caudill

Other Investigators: Lois Frost

Cooperating Units: None

Man Years

Total:	3 11/12
Professional:	3/4
Other:	3 1/6

Project Description:

Objectives: (1) To identify and describe patterns of parental care and child behavior in Japanese and American families. (2) To determine the relationship of these patterns of behavior to personality development, psychopathology, culture, and social structure in the two countries.

Methods Employed: The basic design of the study and methods used have been described in detail in previous reports. Briefly, this is a longitudinal observational study of the behavior of parents and children in the home over the first six years of life in Japan and the United States. During 1961-64, 30 Japanese and 30 American middle-class mother-infant pairs were selected for observation. The infants were first-born, normal babies, and were three-to-four months of age at the time of observation. The first 20 Japanese and the first 20 American cases were selected for follow-up study at 2½ years of age, and observations in the home were completed during 1963-1967. These same children were studied for a third and final time at 6 years of age during 1967-70, and all observations have been completed.

The great bulk of the time during the current year has been spent in the detailed task of coding the data from the observations

at 2½ years of age. In addition, as indicated under findings, comparisons were made between the data from infancy on the Japanese and American cases and data on a series of Japanese-American cases provided by Mrs. Lois Frost of Corvallis, Oregon.

Major Findings: This year we were able to obtain observational data on 21 mother-infant pairs from a third cultural group, the Japanese Americans. This group is of particular theoretical importance for our research because the infants are genetically Japanese but, as they are part of the third generation of babies of Japanese ancestry to be born in this country, they are being reared by parents whose values and behavior patterns are now very similar to those of white middle-class Americans. Thus, the Japanese-American group provides us with a unique combination of genetic and cultural factors which can be used to test earlier findings and conclusions concerning differences in the behavior of Japanese and American infants at three-to-four months of age.

Earlier findings from the comparison of the Japanese and the American data show that American babies are more physically active and do more vocalizing--particularly more happy vocalizing--and these behaviors are correlated with the greater amount of lively chatting to babies done by American mothers. Japanese babies are more physically passive and do more unhappy vocalizing, and these behaviors are correlated with the greater amount of vocal lulling, carrying and rocking of babies done by Japanese mothers. From these, and other, findings we concluded that by three-to-four months of age the infants in the two cultures had already learned (or had been conditioned) to behave in culturally distinctive ways. Such a conclusion has major theoretical implications for the understanding of personality development and for knowledge about the transmission and persistence of cultural patterns of emotion, cognition, and behavior in human groups.

Against the interpretation just given, however, one might argue that the behavioral differences between the Japanese and American infants may be due more to group genetic factors than to cultural learning or conditioning. And this is where the Japanese Americans fit in as they are a crucial group for testing this argument. If group genetic factors are more important, then the behavior of the Japanese-American infants should be closer to the behavior of the Japanese infants in showing greater physical passivity and more unhappy vocalization; but if cultural conditioning by mothers is more important, then the behavior of the Japanese-American infants should be closer to the behavior of the American infants in showing greater physical activity, greater total vocalization, and especially more happy vocalization. As indicated by the findings discussed below, the main result of these comparisons shows that the Japanese-American

infants and mothers primarily behave like the American infants and mothers, and the conclusion to be drawn from this is that cultural conditioning has a greater influence on infant behavior than does the operation of possible group genetic factors.

Because of the reasons just given, the principal investigator has for some years wanted to collect data on a series of Japanese-American babies, and how we were able to obtain these data this year is a pleasant example of scientific serendipity. In 1969, Mrs. Lois Frost was a graduate student in anthropology at Sacramento State College. She read an article coming from this project (Caudill and Weinstein in Psychiatry 32: 12-43, 1969) comparing the behavior of Japanese and American mothers and infants, and decided to do a similar study on Japanese Americans for her master's thesis. Using the same methods, she carried out observations during 1969-70 in Sacramento, California, in the homes of 21 Japanese-American mothers having a three-to-four month old baby. As was true in gathering the observations in the Japanese and American cases, data on the ordinary daily life of the Japanese-American infants were obtained by time-sampling, one observation being made every fifteenth second over a ten-minute period in terms of a predetermined set of categories concerning the behavior of the mother (or other caretaker) and the behavior of the infant, resulting in 40 equally spaced observations. There was a five-minute break between observation periods, and ten periods were completed on each of two days, giving a total of 800 observations for each case.

After collecting her data, Mrs. Frost wrote to the principal investigator telling him of her study and offering to share her material with him. He arranged to visit her for consultation and for the purpose of doing a reliability check. Together they carried out observations in the homes of four additional infants in order to obtain data for testing inter-observer reliability and degree of observer bias. Upon analysis, these tests proved to be within satisfactory limits.

All of the Japanese-American families are middle class as measured by the occupation and education of the husband, and the education of the wife. In this regard, the Japanese-American families are comparable to the families in the Japanese and American samples. Among the 21 Japanese-American infants, 7 are male and 14 are female, and 11 are first-born and 10 are later born. Because the sex distribution is more equal and all infants are first-born in the Japanese- and American samples, we did a complete internal analysis of the Japanese-American data using sex and birth order as independent variables. The results are almost entirely negative. We proceeded, therefore, with the direct comparison of the data from the three cultural groups.

The basic procedure in analyzing the data was to make three paired cultural group comparisons (Japanese Americans with Japanese, Japanese Americans with Americans, and Japanese with Americans) using the sets of predetermined behavioral categories for the infant and the mother as the dependent variables, and using sex of infant and cultural group as the independent variables. The statistical technique employed was multivariate analysis of variance, and all results mentioned here are significant at less than the 0.05 level using a two-tailed test.

In the three sets of paired comparisons, none of the interactions are significant, and there are no findings by sex of infant. Cultural differences, however, are very important in each of the comparisons, and the general patterning of these findings is discussed below.

In the area of basic caretaking for the infant's biological needs, the behaviors of the mothers and infants are remarkably similar in the three cultural groups. There are no differences in any of the paired comparisons in the amount of time infants are asleep or awake, or in the amount of time spent by infants in sucking on breast or bottle (these modes of drinking are combined into a variable which may be called "attempting intake of milk"). The American mothers, however, do more feeding of semi-solid food to their infants than do Japanese mothers, and Japanese-American mothers even exceed the American mothers in this regard. Because of this, Japanese-American mothers are spending more time than mothers in either of the other groups in feeding their babies, and probably as a result they are also doing more diapering and burping. The mothers in all three groups spend the same amount of time in looking at, and in providing other care (wiping face and mose, giving medicine and vitamins, etc.) for their babies.

In the area of what may be called "styles of interaction between mother and infant" the behaviors are culturally much more distinctive. Unlike Japanese mothers, American and Japanese-American mothers do much more lively chatting to their babies; and unlike Japanese babies, American and Japanese-American babies are more physically active, have a greater amount of total vocalization, and dommore happy and less unhappy vocalization. These behaviors are, moreover, highly intercorrelated in the American and Japanese-American data, but this is not so in the Japanese data. In these regards, then, the Japanese-American mothers seem to have become like the American mothers, and the infants have responded accordingly.

At the same time, however, there are a number of behaviors in which the Japanese-American mothers are closer to the Japanese mothers, and they seem to have retained elements of a Japanese style of mothering as this has been passed down from one generation

to the next in this country. Unlike American mothers, Japanese-American and Japanese mothers do more playing with their babies, and also more verbal lulling and carrying of their babies; and unlike American babies, Japanese-American and Japanese babies do less playing by themselves, and less sucking of fingers and other non-nutritive objects.

In general, then, the greater activity, total vocalization, and in particular happy vocalization, of the American infant in contrast to the Japanese infant do not seem to be genetic in origin because the Japanese-American infant is like the American infant in these regards even though he is genetically Japanese. Equally, it would seem that both cultural change and cultural persistence are operating to influence the behavior of the Japanese-American mothers and their babies. On the whole, Japanese-American mothers have come to behave like American mothers, but in some respects they have retained elements of their Japanese cultural heritage. And, as might be expected, the Japanese-American babies respond appropriately and, even into the fourth generation of Japanese-Americans living in the United States, learn to be not only like white middle-class American babies, but also like middle-class Japanese babies in some regards.

Scientific Significance: This research will help to provide precise measures of parental care and of infant and child behavior in several cultures. It should also help in determining how soon, and in what ways, essentially biological activities of the infant (sleeping, touching, looking, vocalizing) are influenced by cultural pressures mediated mainly through the mother or other major caretaker. As the study progresses, it should contribute to understanding of personality formation, value orientations, and family dynamics in different cultures, and thus aid in the further definition of what are "normal" and "abnormal" processes in human social and psychological development.

Proposed Course of Project: The comparison of the Japanese-American, Japanese, and American data from infancy will be prepared for publication. Comparative analysis will be begun on the Japanese and American data from 2½ years of age. A major portion of the coming year will be devoted to the coding of the data from 6 years of age.

Honors and Awards: None

Publications:

Caudill, W.: The study of Japanese personality and behavior. In Norbeck, E., and Parman, S. (Eds.): The Study of Japan in the Behavioral Sciences. Houston, Rice University Press, 1970. Published as a separate number in a series: Rice University Studies, Vol. 56, No. 4, pp. 37-52.

Caudill, W.: Report on the work of Part One: consequences for children of varying family patterns. In Hill, R., and Konig, R. (Eds.): Families in East and West: Socialization Processes and Kinship Ties. Paris, Mouton, 1970, pp. 3-11.

Caudill, W., and Weinstein, H.: Maternal care and infant behavior in Japanese and American urban middle class families. In Hill, R., and Konig, R. (Eds.): Families in East and West: Socialization Processes and Kinship Ties. Paris, Mouton, 1970, pp. 39-71.

Caudill, W.: Cultural patterning of sexual behavior in American and Japanese societies. In Kretchmer, N., and Walcher, D. N. (Eds.): Environmental Influences on Genetic Expression. Washington, D. C., U. S. Government Printing Office, 1970, pp. 191-197.

Caudill, W.: Tiny dramas: vocal communication between mother and infant in Japanese and American families. In Lebra, W. P. (Ed.): Mental Health Research in Asia and the Pacific, Volume Two. Honolulu, East-West Center Press, in press.

Serial No. M-S-P(C)-38
1. Socio-environmental Studies
2. Personality and Environment
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Interrelationships between Social Interaction, Psychological Functioning, Perceptual Style, Physiological Arousal and Personal History Factors Among Schizophrenics

Previous Serial Number: Same

Principal Investigator: Carmi Schooler

Other Investigators: Monte S. Buchsbaum

Cooperating Units: Laboratory of Psychology, NIMH; Saint Elizabeths Hospital

Man Years

Total:	3/4
Professional:	1/4
Other:	1/2

Project Description:

Objectives: The objective of this series of studies remains the attempt to explain the variance found in earlier experiments with schizophrenics by discovering the interrelationships among those variables which these earlier studies indicate are central to an understanding of schizophrenia: task performance, physiological arousal, perceptual style, social behavior, symptomatology and psychiatric history.

Methods Employed: Several approaches are presently being followed. (1) The level of physiological arousal and task performance under different social conditions of both schizophrenics and nonschizophrenics have been measured and related to variations in perceptual style and personal history. (2) A major study has been initiated which involves the interrelating of measures of evoked response, perceptual style, skin temperature (a measure of physiological arousal) and symptomatology. (3) In order to facilitate the continuance of both of the above types of study, an attempt is being made to develop a generalized computer program to simplify the analysis of measures of physiological arousal and to relate these measures to each other and to other aspects of the experimental situations.

Major Findings: This year there are no new findings; the year has been devoted primarily to the initiation of the above-mentioned study of the interrelationships between evoked response, perceptual style, skin temperature, and symptomatology, and to the preparation of final drafts of papers whose substance was reported in previous annual reports.

Scientific Significance: Since clinicians had long noted that social withdrawal appeared to be a marked feature of schizophrenia, and experiments by Schooler and others had demonstrated that the greater the degree of social contact the greater the decrement in the schizophrenic's functioning, it seemed reasonable to initiate a series of studies seeking the key to the schizophrenic's malfunctioning in his reactions to his social environment. In one of these studies, Schooler and his co-workers were able to establish through direct observation of ward behavior that lack of social interaction is, indeed, one of the characteristics which differentiates schizophrenics from other hospitalized mental patients. Furthermore, the results of another study indicate that this lack of interaction is mirrored by an expressed preference for avoiding entanglements with others. Additional studies in the series have shown how the schizophrenic's performance in standard psychological experiments is affected by orientations which are at least partially the results of his past social experiences. Thus, one study indicates that the effect of positive or negative evaluation on verbal-paired associate learning is a function of the subject's self-esteem; subjects with low self-esteem doing especially poorly on tasks requiring novel associations after being given positive evaluations of their performance dissonant with their negative self-image.

Several other studies point to the possibility that society's general norms as to sex roles have differentially affected male and female schizophrenics' willingness to show or receive signs of positive or negative feelings. Their findings are congruent with the supposition that in our culture the expression of emotion, and particularly of affection, is an area of conflict for men, while for women a major area of concern is fear of evoking the hostility of others.

The possibility that social psychological factors can even affect psychophysiological relationships is indicated by the findings of another study which show that the social nature of the situation can affect the direction of the relationship between physiological arousal and task performance. This interaction between the social situation, the schizophrenic's functioning, and his physiological reactivity pointed to a general weakness in the way this series of studies had been carried out until that point. They had been conducted primarily from one research perspective and were concerned with only a limited area of the individual's functioning. Although the findings were significant they had not been very powerful possibly

because differences in the nature of physiological reactivity of different subgroups of schizophrenics may have produced contrasting, or at least differing, results.

A review of the literature revealed that the general concentration on one aspect of the individual which had marked these social psychologically oriented studies was at least as pronounced in studies in other areas. It was therefore not at all surprising that the weak results which marked the series of social psychological studies were at least as powerful as the results of studies approaching the problem of schizophrenia from other directions. Thus, for example, years of search for biochemical differences between schizophrenics and others have resulted in no reliably replicable findings. The effects of genetics appear to be less and less powerful, the better controlled the study. Putative social class differences between schizophrenics and others do not seem to exist under all conditions and where they do exist it is far from clear whether such differences are related to the cause of the disease or its effects. Those theoretically based systems of classifying patients into subgroups which have been investigated have not produced consistent findings and, in fact, the most highly touted mode of classification--pre-morbid adjustment--proved totally unable to pass the test of controlled replication.

The lack of findings has certainly not been due to any lack of theories or hypotheses. Hypotheses have been brought forth with the ease of the proverbial blind men describing the elephant, e.g., those studying tails describing the elephant as long, thin, and floppy; those studying problem-solving seeing the essence of schizophrenia in thought disorder.

Two courses seem to be presently open. One can keep on making hypotheses from limited bodies of data, hoping to achieve the flash of insight which will permit us to see from our limited point of view what the elephant is really like, or one can go ahead with the duller task of trying to do studies which attempt to coordinate data from many vantage points in order to get enough information to make meaningful hypotheses possible. The present series of studies represents an attempt to follow the second of these courses with the aid of modern multivariate techniques and computer technology. It thus involves the interrelation of five different types of variables which seem to be the most promising in terms of their possible etiological significance, their consistency in predicting schizophrenic responses, and their amenability to experimental manipulation. These five classes of data are (1) perceptual functioning, (2) central and autonomic nervous system arousal, (3) task performance, (4) social interaction, (5) psychiatric symptomatology and history.

Studies were undertaken which involved the replication and evaluation of earlier studies of schizophrenia in these five areas in a way which would permit the examination of their interrelationships

among different schizophrenic subgroups. These studies of the investigator and his collaborators are now starting to show that many of the previously contradictory findings in the area of schizophrenia research have been due to an incomplete comprehension of the complexity of the interrelationships between psychiatric symptomatology, patterns of physiological arousal, and perceptual and social functioning among different types of patients. Thus, for example, it appears that among acute schizophrenics the presence of a high level of perceptual stimulation and an active internal life is associated with a high level of intellectual performance. On the other hand, among chronic schizophrenics those who have active internal lives tend to be nonreceptive to perceptual stimuli, augmentation of the experienced intensity of external stimulation in chronic schizophrenia only occurring when the individual's emotional life is "burnt out." The fact that, in contrast to acute schizophrenics, chronic schizophrenics who have active internal lives tend to be nonreceptive to perceptual stimuli suggests that for such patients the reduction in the experienced intensity of external stimuli may be a neuroperceptual adjustment which permits the individual's internal life to be maintained.

Proposed Course of Project: Data collection will be continued and analyses of already collected data will be continued and the results prepared for publication in a scientific journal.

Honors and Awards: None

Publications:

Schooler, C. and Silverman, J.: Differences between correlates of perceptual style and Petrie task performance in chronic and acute schizophrenics. Perceptual and Motor Skills, 32: 595-601, 1971.

Serial No. M-S-PS-1
1. Socio-environmental Studies
2. Personality and Stress
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Health Orientations of Parents and Children

Previous Serial Number: Same

Principal Investigator: John D. Campbell

Other Investigators: Susan C. Quillian, Margaret F. Luther, Sandra M. Duchnok

Cooperating Units: Children's Hospital, Washington, D. C.

Man Years

Total:	3
Professional:	1
Other:	2

Project Description:

Objectives: To study health orientations of family members. Specifically, the goals of the study are, first, to describe systematically the patterns of variation in family members' attitudes, values, beliefs, perceptions, and behavior concerning phenomena of illness and health; and second, to examine ways in which selected personal and situational factors relate to health orientations. Relevant to the attainment of these objectives are the following three assumptions basic to the study: (a) an individual's orientation to health and illness is embedded in interactive processes; (b) such orientations are at least in part learned; and (c) to a considerable extent such learning takes place as an aspect of routine family relationships.

Methods Employed: Information on 264 hospitalized children and their mothers was obtained by use of focused interviews, questionnaires, and rating scales. Interviews with children and mothers, and questionnaires completed by the mothers provide data on (a) aspects of their definitions of illness, (b) reports of their own and other family members' feelings and actions when ill, (c) their attitudes and beliefs about illness prevention and treatment, (d) their values in selected areas not directly relevant to health, and (e) views about appropriate standards of behavior: what should or should not be done in circumstances pertaining to illness and health. Ratings, made by nurses in the hospital setting, appraise children's emotional dependence and anxiety.

Major Findings: Construction of multi-item scales, a task in process when the preceding annual report was submitted, has been completed. Factor-analytic procedures employed in obtaining such scales revealed that the patterned organization of conceptual dimensions linking children's appraisals of specified illness-relevant measures showed considerable similarity to the corresponding factor structures derived from mothers' appraisals. This between-group dimensional correspondence is both methodologically reassuring and substantively informative.

From a methodological perspective it ensures that alternative bases for weighting an individual's responses lead to very similar outcome scores: correlations of one set of factor scores of children's responses based on loadings derived from factor analysis of children's data only with a second set of scores of their responses to the same items with loadings now stemming from analyses in which both children's and mothers' data were independently included were typically greater than .90. (Corresponding alternative scoring of mothers' data also yielded correlations with similar high magnitude.)

On a substantive level, the similarity between factor structures for mothers' and children's data emphasizes the fact that the diverse elements contributing to selected aspects of children's health orientations are conceptually organized in a fashion similar to that found among the mothers: the generationally separated groups share common judgmental frameworks, even though the evaluations themselves may differ from group to group.

The view that health orientations of children will be similar to those of mothers is simply a specification of the generally accepted idea that an important part of socialization involves processes whereby growing children increasingly adopt frames of reference congruent with those of their elders. Previous annual reports contained preliminary statements documenting a number of age-developmental trends in health orientations. Recently completed analyses provide further information and additionally suggest the possibility that at least two different routes may lead to intergenerational congruence of health orientations.

Perhaps the most likely path along which children move in their approach to adult orientations is one in which the parental perspective provides the prototype for the views adopted by the child: pairwise comparisons of aspects of mothers' and children's health orientations should show that parent-child similarity in perspective is greater when views of older children and their mothers are compared than when younger children constitute one of the information sources. In many instances the data of the present study conform to this model. The greater congruence of mothers' and older children's views are evident in such diverse areas as assessments of the child's functioning in the sick role, his health

relevant risk taking, assessment of responsibility for his illness, general health-relevant standards, and the like. Such data suggest that the child learns his health orientations at his mother's knee.

That the picture is more complicated than that is, however, evident when one employs two different perspectives to examine age-developmental trends in a centrally relevant area, the individual's conceptualization of illness. Comparison of group profiles of thematic emphases in illness definitions reveals some general similarities between mothers and children: when definitional themes are ranked on the basis of likelihood of their being reported, the correlation between rank orderings for mothers' reports and those of the children is .55. Although the general definitional perspectives of older and younger children are quite similar (with a rank correlation of profiles for these two age groups equalling .75) the thematically typical definition of the older children is considerably closer to the general maternal view than is the comparable comparison of the typical profiles of mothers and younger children (rs are .69 and .43 respectively). When, however, instead of comparing group profiles, concordance of mother-child thematic report was examined, the apparently reasonable expectation that pairs would report similar themes was, surprisingly, not substantiated. With older and younger children alike, mother-child comparisons yielded little other than chance thematic predictability. It is thus likely that some of the consensus across age groups in illness definition more likely results from a general social accretion than from the specific mother-to-child transmission of maternal illness concepts.

Scientific Significance: This research provides information about a specific area that is currently only inadequately covered; it should lead to a more systematic picture of health orientations and factors associated with such orientations than is now available. The potential value of the research is not, however, restricted solely to the confines of sickness and health. Within the framework of the study, such general social psychological issues as role learning, developmental changes in family relationships, and role behavior in stressful conditions can be treated. The phenomena of illness and health can be viewed as representing aspects of these general issues.

Proposed Course of Project: Statistical processing of information from interviews, questionnaires, and ratings is under way. Upon completion of data analysis, research reports will be prepared for publication in scientific journals.

Honors and Awards: None

Publications: None

Serial No. M-S-S-12
1. Socio-environmental Studies
2. Section on Social Structure
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Developmental Study of the Self-Image

Previous Serial Number: Same

Principal Investigators: Morris Rosenberg and Roberta G. Simmons

Other Investigators: None

Cooperating Units: None

Man Years

Total:	2 1/12
Professional:	1
Other:	1 1/12

Project Description:

Objectives: To learn how children's self-images change as they grow older and to gain increased understanding of the social factors that influence self-image formation. While most previous systematic research has focused on self-esteem, the present investigation considers a number of other aspects of the self-image as well: degree of self-consciousness; preoccupation with the self; the quality of self-detachment; stability of self-concept; "front" or "presenting self"; committed and idealized images; development of ego-extensions; and other aspects of the self-image. The aim is to understand how these aspects of the self-image develop; to examine their relationships to a range of social conditions and experiences; and to learn how they are associated with other psychological states, such as anxiety, vulnerability, and depression.

Methods Employed: Structured and open-ended interviews. A stratified random sample of 1910 children from the third through the twelfth grades in a large urban school system was interviewed. Additional brief interviews were conducted with 400 parents to obtain certain essential background information.

Major Findings: Two central areas of analysis of the data have been pursued: (1) Children's views of the system of social stratification,

from the viewpoint of sociological functionalism; (2) the self-esteem of black and white children.

(1) Children's perceptions of the stratification system: the data on this topic have now been analyzed within the theoretical framework of sociological functionalism. According to the functionalists' classic theory of stratification, the system of occupational prestige and income differentials are vital in motivating persons to sacrifice the time, energy, and resources required to train for complex jobs functionally indispensable to the society. It is apparent, however, that the mere existence of a system of unequal rewards and privileges is not in itself sufficient to induce children to acquire the training and utilize the talents necessary for ultimate occupational functioning. Certain status and class perceptions and attitudes are also required to generate the required motivation.

The first condition is that children must be aware of the system of occupational prestige in the society. Our data indicate that this condition is eminently satisfied. As early as the elementary school stage, children are found to rate occupations in an order almost identical to that of high school pupils and, indeed, of adult samples. Using selected occupations from the North-Hatt scale, we find that even among the third graders, the Spearman rank correlation with the adult data is .93 and the Pearson correlation is .94.

A second functional requirement deals with the view of the occupational structure. The motivation to strive must rest on the view that the individual has a reasonable chance of realizing his aspirations. Our data show, in fact, that most children do not believe that equal opportunity exists for all; about two-thirds feel that socioeconomic, racial, or ethnic disadvantages exist. But what is socially functional is the fact that most of these children feel that they personally have as good a chance to get ahead as most others and nearly two-thirds expect to realize their goals fully. Furthermore, they are confident of intergenerational mobility. Over three-fifths of the high school children expect to be richer than their fathers and over four-fifths aspire to higher occupational status. The older children are more likely than the younger children to expect to surpass their fathers, not so much because their own aspirations have risen as that their judgments of their fathers' statuses have fallen.

The existence of a stratification system generates the structural potential for class conflict, a condition dysfunctional for the stability of the system. Certain attitudes may, however, retard this development. One would be a low awareness of the nature of the stratification system; another would be class identification which does not accord with one's objective position in the socioeconomic order. Our data indicate a widespread vagueness among these children about the nature of the social class system and a great deal of

inflation of one's own status position. Furthermore, it turns out to be the advantaged children who have the highest level of class awareness and the most accurate class identification; they, of course, have the least objective incentive for challenging the system. Thus, a characteristic set of attitudes, differentially distributed in the population, operate to mitigate the danger of class conflict immanent in the stratification system.

(2) Self-esteem of black and white children: The analysis of black and white children's self-esteem this year has focused on three themes: (1) academic performance; (2) educational and occupational aspirations; (3) measurement validity.

In agreement with numerous other studies, our sample data show poorer school performance among black children. This difference appears to be small at the elementary level, but widens during junior high and widens further in senior high school. At the secondary school level, school grades are found to be related to self-esteem among both black and white children, but this relationship is weaker among blacks. Three defense mechanisms, focusing around the device of selectivity, appear to contribute to this result: (a) Selective interpretation--While there is generally a strong relationship between school marks and the child's assessment of how "smart" he is, this relationship is weaker among black children; the black child is less likely to "interpret" his school marks as an indication of how intelligent he is. (b) Selective perception--The poorer the child's grades, the less likely the child is to believe that his parents consider him intelligent; but this is less true of black than of white children. (c) Value selectivity--While the black child who does poorly in school is less likely to "care" about whether or not he is intelligent, this is not true of similar white children; they care at least as much as other whites. Psychological selectivity thus operates to protect the self-esteem of black children. It is also found that, at the secondary school level, black children in integrated schools have higher marks than those in segregated schools, which will have important economic consequences for the future.

Turning to economic and educational aspirations, our data have been found to agree with most research showing that black children's aspirations are just as high as those of whites. This surprising finding has never been satisfactorily explained. Viewing the matter from a developmental perspective, however, we find that in nine out of eleven aspiration comparisons, increasing age brings an erosion of aspirations of black children, relative to whites. The two exceptions deal with intergenerational mobility. Black children are more likely than whites to believe that they will surpass their fathers' achievements; this is not unrealistic in light of the very low socioeconomic position of most of their families. Although black children's aspirations are just as high as those of whites--

they are just as likely to want to enter high status occupations--there is evidence to suggest that they may have a lower "floor of satisfaction," i.e., they are more likely to feel satisfied if they end up at the higher manual or lower white collar levels. These findings suggest that the future gap between aspirations and achievement among blacks may not be as great as initially anticipated.

Since there is no standard measure of self-esteem in the literature, a detailed investigation of the validity of the measuring instrument has been undertaken. The measure employed in this study is a six-item Guttman scale whose Coefficient of Reproducibility is 90.2 percent and Coefficient of Scalability is 67.6 percent. The measure thus possesses internal reliability. The evidence indicates that the measure has face validity, trait validity, construct validity, and satisfies the "interchangeability criterion." Second, it yields the same results whether the interviewer is black or white. Third, at each age level, the Coefficients of Reproducibility are virtually identical for black and white children. Finally, all ten predictions involved in the construct validity of the scale are borne out for both black and white children. The data thus suggest that the self-esteem measure is valid for children of both races.

Scientific Significance: Problems of the self-image are often involved in mental health and illness. Among the major social factors contributing to self-image formation are the individual's social class and his race. These studies shed light on the social psychological processes involved in responding to the stresses inherent in low social status, whether this status is based on socioeconomic position or on race.

Proposed Course of Project: Data analysis will continue through the coming year. It is anticipated that the focus will shift to a consideration of certain other aspects of the self-image; we hope to learn how these develop over time and whether the rate and direction of development is influenced by one's location in the social structure.

Honors and Awards: None

Publications:

Simmons, R. G. and Rosenberg, M.: Functions of children's perceptions of the stratification system. American Sociological Review, in press.

Serial No. M-S-SP-3
1. Socio-environmental Studies
2. Section on Social Process
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Variables Affecting Twin Birth Frequencies

Previous Serial Number: Same

Principal Investigator: Gordon Allen

Other Investigators: None

Cooperating Units: In prior years data have been supplied by the National Center for Health Statistics, Public Health Service. New data will be obtained if possible from the Perinatal Research Branch, NINDS.

Man Years

Total:	1/8
Professional:	1/8
Other:	0

Project Description:

Objectives: To develop hypotheses to explain temporal and geographic variations in plural birth frequencies and to test any hypothesis for which appropriate data can be obtained.

Methods Employed: Birth intervals preceding same-sex and opposite-sex twin births and singleton births will be adjusted for age and parity. Use will also be made of information on contraception and on intervening abortions. Significant differences among the adjusted birth intervals will rule various hypotheses in or out.

Major Findings: None this year.

Proposed Course of Project: The prospect of securing critical data has led to a planned extension for one more year.

Honors and Awards: None

Publications:

Allen, G.:and Schachter, J.: Ease of conception in mothers of twins. Social Biology, in press.

Serial No. M-S-SP-4
1. Socio-environmental Studies
2. Section on Social Process
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Individual Differences in Survival and Reproduction Among Old Colony Mennonites in Mexico

Previous Serial Number: Same

Principal Investigators: Gordon Allen and Calvin Redekop (non-PHS)

Other Investigators: None

Cooperating Units: Goshen College, Goshen, Indiana

Man Years

Total:	1-3/4
Professional:	3/4
Other:	1

Project Description:

Objectives: To demonstrate the presence or apparent absence of selective survival and reproduction with respect to individual behavioral characteristics. Also to study natural patterns of marriage and reproduction in a relatively simple agricultural society of traditional European type.

Methods Employed: The population under study consists of about 13,000 German-speaking Mennonites in a politically integrated cluster of villages in northern Mexico. These people were selected because of their simple and uniform culture insulated from mass communication media and because of their apparently unrestricted fertility. Also important was the fact that, unlike some similar religious isolates, this society supports a considerable degree of economic competition.

Information was gathered by means of a combined census and questionnaire that reached a third of the population. This has been supplemented with photographs of all vital records kept by the church, a public list of farmers and their holdings, a list of all village and church leaders in the 40-year history of the population, and records of Mennonite births in local hospitals. Interviews were conducted by the investigators and by a Canadian Mennonite with the

aid of cooperative local men. This material defines the background of attitudes toward community problems, overpopulation, and birth control.

The data are now being edited for errors and inconsistencies. Linking of information from diverse sources concerning each family has been started and will be continued in conjunction with the editing process. Analysis will begin with cross-tabulation and end with multivariate analysis.

Major Findings: None this year.

Scientific Significance: Natural selection is apparently the sole agent responsible for the progressive evolution and maintenance of human mental capacities. The study of selection in a pre-industrial European society may indicate some of the influences that have produced present genetic tendencies and draw a base line for future studies of selection under modern conditions.

Proposed Course of Project: Analysis of the data is expected to occupy between two and four years.

Honors and Awards: None

Publications:

Allen, G.: Within group and between group variation expected in human behavioral characters. Behavior Genetics, 1: 175-194, 1970.

Serial No. M-S-SP-5
1. Socio-environmental Studies
2. Section on Social Process
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Social Origins of Stress

Previous Serial Number: None

Principal Investigator: Leonard I. Pearlin

Other Investigators: Frederic W. Ilfeld, Jr., and Albert J. McQueen

Cooperating Units: None

Man Years

Total:	4 1/6
Professional:	2 1/3
Other:	1 5/6

Project Description:

Objectives: This study examines the connections between social conditions, personal stress and enduring mental states. By stress we refer to any emotional burden experienced by individuals from which they attempt to remove themselves. In contrast to the previous studies that have emphasized unusual and extreme threats to safety, we are directed toward daily events and experiences in the lives of people that can be traced back to basic features of social organization.

Our attempt to unravel the complex connections between the organization of a society and the inner stresses of its members begins with the fact that people have several social statuses, some of them assigned on the basis of such criteria as class, race, age, and sex. A variety of constraints and imperatives converge on the occupants of statuses, and the patterns of behavior that result constitute a social role. Much of what a person learns as a member of his society and many of the experiences that have an important impact on his development vary with his statuses and roles. Consequently, people having different statuses and roles become different kinds of people, though they are members of the same society. The more highly differentiated the organization of the society, the more differentiated are its individual members.

Personal stress enters this picture simply because contemporary societies are imperfectly organized; that is, the statuses

and roles that one has in different social institutions are often not complementary or integrated. One may acquire a valued self-image in one area of his life, for example, which is denied expression in another; one may be brought into close interactions with others whose interests and values are in sharp conflict with his own; one may learn to strive after goals from which he is blocked; one may learn to strive after goals from which he is blocked; one may be expected to act in a way inconsistent with his precepts, and so on. These conditions illustrate imperfections in the organization of society, but they are eventually reflected in the actions and feelings of individuals. Our major objective is to explicate this process.

Methods Employed: The work will pass through several overlapping phases. The first has involved approximately forty intensive, unstructured interviews, many of them with black residents of center city areas. On the basis of what has been learned from these interviews, we are currently passing into a second, more structured phase, in which questions are being developed, tested, and revised. This is in preparation for the third phase of our data collection, which will be a large-scale sample survey, national in scope, and employing a standardized interview schedule.

Major Findings: Although research into stress has a long history, there are no previous studies whose scope or terrain are the same as this. Because of this the interviews have been most useful in clarifying and enriching these conceptual elements in the stress process: (1) The nature of social conditions potentially productive of stress; (2) Mediating factors that regulate the impact of these conditions on individuals; (3) The subjective experiences of stress itself; (4) The means by which people cope with stress; and (5) Enduring mental states that may result from chronic stress. These are discussed in order.

A number of social conditions potentially productive of stress have been identified from our exploratory interviews, but three stand out as major types. One involves a conflict between elements of a person's self-image and the ways he must play his social roles. Basically this condition arises when the prescriptions and proscriptions regulating an individual's behavior do not allow for the authentic expression of elements of the self that the individual considers important. This has been voiced in the interviews in a variety of ways: by the woman who reports that around men she acts stupid so that they will accept her; by the individual who feels that his friends don't know him as he really is; by the wife who must act submissively, though she has a higher regard for her own decision-making abilities than her husband's; by a young man who sees himself as a champion of the underdog and whose job it is to collect delinquent bills, and so on.

A second type of stress-arousing condition concerns the threat posed by the behavior of others to one's social expectations. Whereas the first type involves the inability of an individual to realize valued elements of his self while conforming to others' expectations, the second involves the failure of others to fulfill the expectations of the individual. Illustrations of the frustration of expectations are sprinkled throughout the interviews, but are especially clear in themes touching on family life. Through the criss-crossing expectations that exist in the family, one hears husbands express discontent with their wives as lovers, wives with their husbands as breadwinners, and parents with their children as scholars.

The third major social condition that antecedes personal stress is the confrontation of obstacles to highly prized goals. Understandably, this experience is no stranger to career-oriented people in their occupation life, and it is not uncommon to those struggling to achieve the material and status rewards that go with upward mobility. Because these goals are cherished by the society and culturally upheld as worthy of our efforts, failure to achieve them is clearly relevant to stress.

Just as the interviews helped in the identification of conditions that may stressfully impinge on individuals, they have also helped in specifying the institutional areas in which these conditions are likely to enter into the experience of individuals. The denial of self-expression, the violation of expectations and the frustration of goal attainment are not experiences that afflict an unfortunate few who happen to be caught in a set of unusual circumstances. These are enduring and repeated features of daily life, probably touching every one, although not with the same intensity. And they are to be found in all the principal social institutions in which one participates and interacts with others. Because of the ubiquitousness of stress, as we conceive it, our search for its origins will not be confined to a single area of life, but will traverse several institutions: the family, occupation, interpersonal relations, and what has come to be recognized as the societal opportunity structure.

The second conceptual issue in the stress process pertains to mediating factors. It is evident that the stresses an individual experiences cannot be predicted directly from the social conditions to which he is exposed. The impact of social conditions will depend on the appraisal that the individual makes of these conditions. The nature of the appraisal determines what the intensity of the stress will be, if any, and how the individual will eventually attempt to deal with the stress. Several specific dimensions of cognitive assessment enter into appraisal. Perhaps most crucial among these is simply the importance individuals attribute to the conditions. Generally speaking, a condition is most likely to result in stress when it occurs in an area of life to which the individual attaches

primary importance; personal stress is least likely to result when the condition is in an area to which the individual ascribes little significance. A second element in appraisal is the matter of mastery, the extent to which an individual feels he can alter or favorably modify an impinging condition. Closely related to this are his perspectives of the future, whether he optimistically regards the conditions of his life as likely to undergo positive change or pessimistically views them as becoming bleaker. Other aspects of appraisal emerged from the interviews, but these are among the most salient.

The conceptualization of stress itself is perhaps the most critical and challenging task to which the interviews were directed. As noted above, we think of it as a noxious emotional state from which relief is sought. We also think of it as a state that is specific and responsive to identifiable conditions and events in the lives of people, rather than as a steady, enduring mental state. In other words, to establish empirical relationships of stress to specific and variable social conditions, it is necessary to think of stress itself as specific and variable rather than as global and persisting. To do this, it is of course necessary to rely on what people can tell us of their inner feelings and on their ability to relate specific feelings to specific conditions and events in their lives. Methodological questions of the accuracy of such information are by no means settled, but it does appear that subjects are able to reflect on these matters with greater ease than one might suppose.

Coping with stress is the fourth major area of our theoretical schema to profit from interviewing. Perhaps more has been written on coping than any other of the social psychological aspects of the stress process; yet there is surprisingly little empirical work from which this study can borrow. However, interviewees' accounts of coping suggest a threefold distinction based on the point in the stress process at which the coping intervenes. Thus, some coping behaviors are seen as functioning to modify the situation. Either by defusing the stress-provoking elements in the situation or by stepping outside the aura of their influence, the individual is protecting himself from emotional distress. Other coping behaviors serve to alter the appraisal process. Some of our subjects suggested that they have reordered priorities or invoked new standards as mechanisms for alleviating stress by changing the perception and meaning of the situations arousing the stress. Finally, some coping is directed primarily toward the management of stress itself. These behaviors serve neither to modify the situation nor its meaning, but to relieve the individual from acute awareness of his feelings of stress.

In addition to these types of behaviors, individuals can be distinguished according to the resources they use in coping.

Specifically, people may seek coping resources in their informal social relations, both inside and outside the family; through formal channels, such as expert help and organized agencies; or they may rely entirely on their own intrapsychic and personal mechanisms. It needs to be emphasized here that just as we are interested primarily in social stress, we are also especially interested in coping mechanisms that are social, those which one learns from his membership in or identification with various groups.

A final conceptual elaboration that has been made is in the distinction of enduring mental states from more specific states of stress. By mental states we mean conditions of depression, anxiety, apathy and other psychological constellations that are relatively independent of time, space and situational variability. Within the framework of this study we see these mental states more as long-term consequences of exposure to stress or as resulting from inadequate coping than as reflecting stress aroused by more current circumstances of one's life.

Scientific Significance: These, then, are some of the conceptual ingredients that have been developed for this study. The study does not take into account all important sources of stress, nor does it necessarily take into account all measures and consequences of stress. Its significance, rather, derives from emphasizing precisely that which has been ignored in past studies. First, no other inquiry has brought together this array of variables under the umbrella of a single study. Hopefully, this will enable us to begin to unfold the process by which basic features of social organization are united with basic features of the inner life of people. Second, it should help to answer the paradox that bothers and mystifies observers of contemporary societies: how do people living under extremely challenging conditions manage to persevere and even flourish, and how can participating members of the society's mainstream become socially and psychologically impaired.

The study is also clearly relevant to prevailing clinical issues. Professionals in the health and mental health fields are recognizing the importance of such social phenomena as class, roles, family, community in both the production and relief of a wide variety of illnesses. Yet there is a striking absence of studies that empirically deal with the intricate relationships among the traditionally clinical and the more social variables. This study should reveal such relationships in large measure.

Proposed Course of Project: The preparation of an interview schedule suitable for a large-scale survey will continue. The most formidable problem in this preparation is the identification of the kinds of information, derivable from interviews, that will adequately reveal the workings of the stress process as we are conceptualizing it. It is expected that the schedule will be ready to be placed in the field in the fall of 1971.

Honors and Awards: None

Publications: None

Serial No. M-S-SP-6
1. Socio-environmental Studies
2. Section on Social Process
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies of Evolution of Reacting Chemical Mixtures Under Nearly Steady-State Conditions

Previous Serial Number: M-S-C-8

Principal Investigator: Gordon Allen

Other Investigators: None

Cooperating Units: None

Man Years

Total:	1/8
Professional:	1/8
Other:	0

Project Description:

Objectives: To explore the possible relevance of simple organic catalysts to the origin of life.

Methods Employed: Laboratory work was concluded in 1964. A small amount of subsequent work has been devoted to reformulating the problem of the origin of life and marshalling arguments for one particular hypothesis.

Major Findings: The exceedingly small probability, according to information theory, of chance origin of a self-reproducing entity and the complexity of conceivable copying mechanisms point to an origin of life that required neither of these phenomena. Such an alternative is found theoretically in reproduction by the environment of compounds that catalyze limiting reactions. This idea was first crudely formulated and published in 1955 by M. Ycas. I have developed it further and named it the bion hypothesis, which follows:

The first regular self-replication of ordered linear polymers on the earth was preceded by a period of evolution by natural selection among simpler organic molecules that did not serve as templates but reproduced by promoting other reactions critical for their own synthesis. These nonliving units of what may collectively have been life can be called "bions."

Bions do not individually have the capacity to mutate or the capacity to accumulate biological information, indispensable for evolution by natural selection. It can be shown, however, that a hypothetical system of bions together with their chemical environment would have both essential capacities.

Scientific Significance: The bion hypothesis, if strengthened, would tend to discourage the research effort being made in several laboratories to produce gene analogs under primitive earth conditions. Even if the hypothesis is not true for the historical origin of life on the earth, the theoretical possibility of natural selection without self-copying may require a reconceptualization of the role of the gene in biology.

Proposed Course of Project: No further work is planned.

Honors and Awards: None

Publications:

Allen, G.: Natural selection and the origin of life. Perspectives in Biology and Medicine, 14: 109-126, 1970.

Allen, G.: A search for mutation in chemical systems at steady state. Nature, 208: 258-260, 1965.

Serial No. M-OD-BBR-2
1. Division of Biological and Biochemical Research
2. Office of the Director
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Characteristics of Membranes in Muscle

Previous Serial Number: Same

Principal Investigator: W. H. Freygang

Other Investigators: R. Gunn

Cooperating Units: None

Man Years

Total:	2.0
Professional:	2.0
Other:	0.0

Project Description:

Objectives: It seems most likely that the initiation of contraction in striated muscle is a consequence of the release of free calcium ions in the interior of the cell. The signal for this release is an electrical one that spreads into the cell through a specialized array of tubules. Therefore, it seems reasonable to suppose that the release of free calcium arises from an electrically induced breakdown in an intracellular barrier to the movement of calcium. Our objective is to find evidence for this postulated barrier by seeking to observe its breakdown by means of changes in its electrical properties.

Methods Employed: Two types of measurement of electrical impedance have been made. In one method a single striated muscle fiber from the semitendinosus muscle of the frog is suspended vertically in a gap of moist air between two pools of Ringer's fluid. The length of the air gap can be varied. The two pools are connected by means of platinum black electrodes to either a Wheatstone bridge or a feed-back impedance-measuring device. The impedance to alternating current is measured as a function of the length of the fiber in the air gap and as a function of frequencies between 2.5 and 100,000 Hz. When an action potential is initiated by means of two additional stimulating electrodes, the alterations in impedance can be measured in both the surface

membrane and the myoplasm.

The other method measures alterations in the surface impedance alone. It consists of a fine platinum wire that is insulated to its tip with teflon. The tip has a coating of platinum black and it is pressed against a single muscle fiber. A Wheatstone bridge is connected between the fine platinum wire and a remote electrode in the pool of Ringer's fluid. When an action potential propagates itself under the tip of the fine platinum wire, the transient imbalance of the bridge shows the variation in impedance of the membrane close to the tip of the wire. Membrane properties and structures in the myoplasm are altered by various solutions. These alterations are observed by standard methods of electronmicroscopy.

Major Findings: An analysis of the longitudinal impedance revealed that most of the intracellular flow of current during an action potential does not flow through the sarcoplasmic reticulum, but rather through the space occupied by the contractile protein. The major increase in membrane permeability during an action potential does not last much longer than the action potential itself and takes place in the surface membrane and transverse tubular system. A smaller increase in membrane permeability is associated with the early after-potential. There is possibly in addition a decrease in the impedance to longitudinal, or myoplasmic current, that occurs during the latency relaxation, i.e., just before the twitch. This component seems to be removed when the transverse tubular system is altered by a Ringer's fluid that has been made hypertonic by the addition of sucrose or by exposure to a mixture of Ringer's fluid and glycerol. Treatment of the muscle fiber with these solutions either eliminates the ability of the cell to contract, or alters it considerably.

Significance to Biomedical Research and the Program of the Institute: These findings illuminate the mechanism of the coupling between the electrical and mechanical activity in skeletal muscle, and perhaps also in heart muscle. A reasonable interpretation of our data seems to us to be that the electrical activity spreads itself over the surface of the fiber and invades the transverse tubular system. Probably calcium enters through the walls of the tubular system. This free calcium may have the ability to increase the permeability to calcium of the sarcoplasm reticulum and allow more calcium to be liberated. This scheme fits with present knowledge and with our data and provides us with a reasonable working hypothesis.

Proposed Course: This project should continue to investigate the mechanism of initiation of contraction by means of other methods, such as caffeine and controlled changes in membrane potential along with the other methods described above. The technical difficulties of controlling the electrical artifacts introduced by movement should be mastered.

Honors and Awards: None

Publications: None

Serial No. M-CM-DN-1
1. Laboratory of Cerebral Metabolism
2. Section on Developmental Neurochemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The mechanism of action of thyroxine and its relation to cerebral metabolism

Previous Serial Number: Same

Principal Investigator: Louis Sokoloff, M.D.

Other Investigators: Patricia A. Roberts, Barbara A. Jant, Elaine E. Kaufman, J. Nunez, Gilman D. Grave, Glenna G. Fitzgerald, John E. Kline and Esther L. Lewis

Cooperating Units: None

Man Years:

Total:	6.25
Professional:	2.75
Other:	3.5

Project Description:

Objectives: The ultimate goal of this project is the elucidation of the role of the thyroid hormone in the maturation and development of the brain and the influence of the hormone in the regulation of cerebral metabolic processes. A necessary intermediate objective is the determination of the molecular mechanisms of the physiological and biochemical actions of the thyroid hormone. Earlier work done previously in this project demonstrated a stimulating action of thyroid hormones on protein biosynthesis. The mechanism of the thyroxine stimulation of protein biosynthesis still remains the primary focus of the project.

Methods Employed: The effects of thyroid hormones on radioactive amino acid incorporation into protein are examined in cell-free protein synthesizing systems from various mammalian tissues, such as liver, brain, reticulocytes, etc. Studies are occasionally carried out *in vivo*, in which the uptake of amino

acids into protein in various tissues is measured in the intact animal or the effects of experimentally induced thyroid disease on various metabolic activities are examined. A wide variety of enzyme purification and assay procedures are also employed.

Major Findings: The major accomplishment of this project thus far is the demonstration for the first time that thyroxine stimulates protein biosynthesis and that this effect is probably primary to most of the generally recognized physiological actions of the thyroid hormones. Thyroxine, administered in vivo or in vitro, stimulates amino acid incorporation into protein in cell-free rat liver preparations. Conversely, hypothyroidism induced by surgical thyroidectomy, results in a reduction in the rate of amino acid incorporation into protein in similar preparations, indicating that the thyroid effect on protein biosynthesis is tonically active and physiological.

The biochemical mechanism of the thyroxine stimulation of protein biosynthesis has been studied in considerable detail in completely in vitro systems. Thyroxine added in vitro to cell-free liver homogenates stimulates amino acid incorporation into protein. The in vitro thyroxine effect is preceded by a 5 to 7 minute latent period preceding the stimulation. This lag can be eliminated by preincubation for a similar amount of time, provided thyroxine, mitochondria, and an oxidizable substrate are present during the preincubation. The thyroxine effect exhibits an absolute requirement for mitochondria and an oxidizable substrate; when these components of the system are replaced by an alternative ATP generating system, such as creatine phosphate and creatine kinase, there is no thyroxine effect although the control rate of amino acid incorporation into protein is essentially the same as with the mitochondrial system. Although the mitochondria are essential for the effect, the thyroxine effect is to stimulate amino acid incorporation into microsomal protein. The thyroxine effect on protein synthesis is not direct, however. It has now been established that thyroxine must first react with some mitochondrial component in an energy-dependent reaction during the latent period to produce an as yet unidentified product(s) which in turn act(s) on the ribosomal protein synthesizing machinery to enhance the rate of polypeptide chain elongation and completion. It has been found possible to carry out this preliminary reaction under controlled conditions, then remove the mitochondria, add the residual soluble components of the mixture to a protein synthesizing system supported by a creatine phosphate-ATP generating system, and observe the thyroxine stimulation. These results indicate the presence of the active factor(s) formed by the interaction of thyroxine and mitochondria which is (are) responsible for the thyroxine stimulation of protein biosynthesis.

The Section has been carrying out a series of experiments aimed at isolating, purifying, and identifying the active agent(s). The results thus far indicate that its production by the thyroxine-mitochondrial system requires a high energy compound, probably ATP. It can be prepared in soluble form and stored at -20°C for several months without loss of activity. It is a small, dialyzable, heat-stable, acid-labile, moderately base-stable, organic, anionic substance. It does not extract into butanol, indicating that it is not an iodothyronine derivative. During the past year studies have been continued to be directed at identifying this active agent both by defining further the properties of the stimulating activity as well as by examining possible candidates for the putative agent. Cyclic AMP, which is known to regulate a number of intracellular metabolic processes in mammalian cells, has been examined as the possible active agent. It has been found that it is capable of stimulating protein synthesis in the same assay system, but its effect is not nearly so great as that of the thyroxine-mitochondrial factor. Furthermore, the thyroxine effect is additive with the cyclic AMP effect over a wide concentration range, suggesting that cyclic AMP is not responsible for the thyroxine-mitochondrial protein synthesis-stimulating activity. The identity of the active factor remains unknown, but significant progress has been made in its purification and characterization.

Work on the factor was temporarily interrupted during the past year to examine a couple of published allegations that thyroxine could stimulate protein synthesis in vitro in systems devoid of mitochondria. Experiments have been carried out which have conclusively demonstrated that these alleged effects are artifactual, and the nature of the artifacts has been identified. These studies restore the validity of the thesis that mitochondria are fundamentally involved in the mechanism of the stimulation of protein synthesis by thyroid hormones.

Thyroxine is known to have profound effects on mitochondrial energy metabolism. It depresses the efficiency of the conservation of energy derived from substrate oxidation in high energy phosphate bonds such as ATP. A number of amino acids, including naturally occurring species, have been found in this laboratory to stimulate mitochondrial respiration and associated phosphorylation, effects which,in general, are quite the opposite of those of thyroxine. The mechanism of this effect may involve processes like those affected by thyroid hormones. Iodohistidine, histidine, and other amino acids have been found to increase the rates of respiration and coupled phosphorylation while thyroxine depresses phosphorylation and the efficiency of oxidative phosphorylation in intact rat liver mitochondria. The

increased rate of phosphorylation observed with these other amino acids is not mediated by effects on adenine nucleotide transport; these amino acids, as well as thyroxine, have no effects on the maximal rates of transport of AMP or ADP into the mitochondria nor on the affinity of the translocase system for the nucleotides. Recent experiments indicate, however, that the effects of the other amino acids may be associated with increases in cation transport into and the ejection of protons out of the mitochondria. Dramatically higher levels of calcium and potassium are found in mitochondria incubated in the presence of these other amino acids. The effects of thyroxine on ion transport in mitochondria have not yet been examined, but such studies will be carried out in the near future. Since ion transport and energy metabolism are known to be closely related in mitochondria, these studies may be of interest and significance in regard to intracellular regulation of energy metabolism as well as to the mechanism of thyroxine action.

Evidence has been accumulating that thyroid hormones may also have important effects on the transport of ions into and out of cells. Experiments have been carried out in this laboratory on the effects of thyroxine on the various microsomal ATPases in rat liver cells. Among them is a Na^+-K^+-stimulated ATPase which is intimately involved in the active transport of Na^+ and K^+ between cells and their external environment. Thyroxine has been found to inhibit the overall microsomal ATPase activity. Attempts to identify which of the various ATPases are affected have thus far shown no specificity. In intact, fresh rat liver microsomes, the Mg^{++}-, the Ca^{++}-, and the K^+,Na^+- stimulated ATPases are all inhibited by thyroxine. Experiments to determine whether these effects have physiological significance in the intact animal will be carried out as soon as an atomic absorption spectrophotometer is acquired, which will permit the analysis of tissue ion concentration in experimental thyroid disease.

Significance to Bio-medical Research and the Program of the Institute: A unique feature of the cerebral metabolism is its apparent lack of response to high circulating levels of thyroid hormone. An understanding of the basis of this unique behavior may reveal information concerning the metabolism of the brain in health and disease. Also, the mechanism of action of thyroxine has been under investigation for many decades, but thus far a satisfactory explanation of the mechanism by which it increases metabolic rate, stimulates metamorphosis and growth, or causes the many disturbances in body physiology and biochemistry in thyroid disease has eluded investigators. The solution of this problem could then lead to fundamental advances

not only in the understanding of how this important hormone regulates bodily functions but also of the nature of bodily processes on which it acts. The clarification of the relationship between its mechanism of action and its effects on development of the brain might also lead to a better understanding of the many biochemical processes underlying the maturation of the brain.

Work has continued on the postnatal biochemical development of the central nervous system, and the role of thyroid hormones in the promotion of development of the brain. Studies are in progress on the mechanisms of the decline of the rates of protein synthesis in the brain with maturation. Thyroid hormones may be involved in this change. It was previously found that the immature brain is thyroxine-sensitive and responds to thyroid hormones with increased energy metabolism and protein synthesis. This thyroxine-sensitivity is lost with maturation because of some still undefined change in brain mitochondria with development, and the possibility that declining rates of protein synthesis are the result of the loss of thyroxine-sensitivity is being examined.

One of the changes which occurs in the mitochondria with development is the level of the enzyme D(-)-β-hydroxybutyric dehydrogenase. This enzyme is low in the brain at birth, increases in early life in parallel with other brain mitochondrial enzymes, such as cytochrome oxidase and succinoxidase, but unlike these others which reach and maintain a constant level throughout adult life, it declines again following weaning. Evidence has been acquired that the changes in the level of this enzyme in brain may be related to changes in the nature of the nutrition at this time in life. The thyroid hormones have also been implicated in these changes. Hyperthyroidism would be expected to retard the changes in both, but these studies are yet to be completed because of difficulties in achieving sufficient thyroid deficiency early enough in young rapidly developing rats before maturation has already been achieved. It may be necessary to study hypothyroidism in another more slowly developing species.

Proposed Course of Project: The project will be continued essentially on the same course already indicated. The major avenues to be pursued are: (1) the attempts to isolate, purify, and identify the product of the thyroxine-mitochondrial reaction responsible for the stimulation of protein biosynthesis; (2) further studies on the elucidation of the mechanism of the stimulation of the protein biosynthetic processes; (3) the further study of the thyroxine inhibition of microsomal ATPase;

and (4) further studies of the biochemical differences between mature and immature brain and the role of thyroxine in the biochemical changes leading to maturation and development of the brain.

Honors and Awards: None

Publications:

Johnson, J. D., Jant, B. A., Kaufman, S., and Sokoloff, L.: Effects of ionic strength on the RNA polymerase activities of isolated nuclei and nucleoli of rat liver. Arch. Biochem. and Biophys. 142:489-500, 1971.

Macon, J. B., Sokoloff, L., and Glowinski, J.: Feedback control of rat brain 5-hydroxytryptamine synthesis. J. Neurochemistry 18:323-331, 1971.

Sokoloff, L., and Raskin, N. H.: Chapter 96. Thyroid Disorders. In Shy, M., Appel, S., and Goldensohn, E. (Eds.): The Cellular and Molecular Basis of Neurological Disease. New York, Lea & Febiger, 1969 (in press).

Sokoloff, L.: Action of thyroid hormones. In Lajtha, A. (Ed.) Handbook of Neurochemistry. New York, Plenum Press (in press).

Sokoloff, L.: Biochemical Mechanisms of the Action of Thyroid Hormones in Nervous and Other Tissues. In Proceedings of the, "Symposium on the Influence of Hormones on the Nervous System," June 22-25, 1970, Brooklyn, N. Y. (in press).

Sokoloff, L.: The Effects of Thyroid Hormones on Protein Synthesis. In Methods in Investigative and Diagnostic Endocrinology. North-Holland Publishing Co., Amsterdam, The Netherlands, 1970 (in press).

Serial No. M-CM-DN-2
1. Laboratory of Cerebral Metabolism
2. Section on Developmental Neurochemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies on regional cerebral circulation and metabolism

Previous Serial Number: Same

Principal Investigator: Charles Kennedy

Other Investigators: Louis Sokoloff, Gilman D. Grave, Jane W. Jehle, John E. Kline and Esther L. Lewis

Cooperating Units: Martin Reivich, M.D., Associate Professor, Department of Neurology University of Pennsylvania, Philadelphia, Pennsylvania

Man Years:

Total:	4.0
Professional:	2.0
Other:	2.0

Project Description:

Objectives:

1. To elucidate the patterns of development of circulation and energy metabolism in various structural components of the developing mammalian brain.

2. To quantify the effects of hyperoxia on nucleic acid synthesis and cell division in the developing brain.

3. To determine whether diphenylhydantoin affects the regional circulation of the brain when given in doses known to increase the seizure threshhold.

4. To continue the development of a method for measurement of regional glucose utilization of the brain in vivo.

Methods Employed:

1. Regional circulation is measured by the autoradiographic ^{14}C-antipyrine technique developed in this laboratory.

2. Nucleic acid contents of brain tissue are measured by the Santen and Agranoff modification of the original Schmidt-Tannhauser procedure.

3. The method for regional glucose utilization is one which has been under theoretical development in this laboratory for several years. This is an autoradiographic procedure in which the non-metabolized analogue of glucose, 2-deoxyglucose is used as a radioactive tracer (^{14}C).

Major Findings:

1. The accumulation of 36 studies over the past 3 years on the regional circulation of the brain of the dog throughout the developmental period permits a detailed study of the maturational changes in blood flow in most of the component structures of brain. Also, maturational changes have been followed in 9 white matter structures. The general pattern, previously observed in a more limited number of studies, is that low levels of blood flow are present at birth; there is a variably steep rise in the first 7 weeks of life depending on the region under observation and, at maturity, blood flow falls slightly in gray matter, and to a much greater degree in white matter. While this general pattern is found in all regions measured, the rate of rise and the age at which maximal perfusion takes place varies markedly in different areas. In the brain stem and cerebellum the early rise is steep with peaks being reached by three weeks of age. In the deep cerebral structures of the hippocampus, the amygdala and hypothalamus, the rates of increase in blood flow are slower, and maximal rates are not found until 7 weeks of age. In the thalamus the early rise is steep for the ventrolateral nuclei which is in contrast to the slower rise in the dorsomedial region. This finding suggests that sensory input from the spinal cord and cerebellar pathways precedes, and perhaps stimulates, maturation of higher motor centers. This priority of sensory maturation is also seen in the slightly earlier rise in blood flow in the sensory cortex compared to the motor cortex. The cortex as a whole is the latest to reach maximal blood flow.

2. In an extension of work started in 1964, measurements were also made in the newborn monkey. These studies provided an

opportunity to compare the values for blood flow in various cerebral structures of the newborn monkey with those of the much-less mature newborn dog. In confirmation of the relationship noted in the developing puppy that early maturation is associated with an increase in blood flow, the neonatal monkey was found to have higher perfusion rates in all structures than had been found in the dog at birth. The difference was particularly striking in the visual and hearing pathways where the functional activity is so markedly different in the two species in the early days of life.

3. It was previously found in this project that exposure to 70-80% O_2 in the new-born period has potent vasoconstrictor effects on the blood flow of various parts of the brain. It has now been found that such exposure, if prolonged, also produces deficits in brain growth, nucleic acid synthesis, and myelinization. These changes in brain development occur in the absence of any comparable effects in the body as a whole. These results also suggest that there is reduced cellular proliferation in the developing brain as a result of high-oxygen exposure; in the rat it can lead to a deficit of as many as 10 million cells. The possibility is being considered that the biochemical changes are the result of the restriction of cerebral blood flow by high O_2 with consequent deficiency of the supply of glucose needed to provide the ribose moieties in nucleic acid synthesis. This hypothesis will be tested by appropriate experiments in the near future.

4. Diphenylhydantoin, an agent known best for its effect in controlling seizure, and, more recently to be effective in treating cardiac arrhythmias, has recently been used in the treatment of cerebral vascular disease. To extend observations made by the principal investigator in human subjects in 1956, which suggested that this agent may be a vasodilator, a study has been undertaken to determine its effect on local blood flow in the brain. The method applied to puppies was adapted to adult rats. In the dose employed (20 mgms/kg) there is some suggestion that two-to-three hours after an intravenous infusion of diphenylhydantoin there is a reduction in cortical blood flow when compared to control levels. The limited number of studies completed to date, however, make this conclusion very preliminary

5. A method to measure the rates of glucose utilization simultaneously in the various component structures of the brain in conscious animals has been under theoretical development in this laboratory for a number of years. The method is based on a model which assumes that ^{14}C-deoxyglucose can be used as a tracer for glucose uptake by tissues with the advantage that its label

will not be lost from the tissue by further metabolism to CO_2. Several alternative equations have been derived from the model which permit the calculation of local glucose utilization provided the history of the arterial glucose and ^{14}C-deoxyglucose concentrations, the duration of infusion of the tracer, and the tissue concentration of ^{14}C-deoxyglucose are known. The former are measured chemically and by liquid scintillation counting; the latter is determined by a quantitative autoradiographic method. Preliminary tests of the method in rats and cats have been extremely encouraging; even without modification of the most naive assumptions, the values which have been obtained are reasonably close to the expected values for local cerebral glucose utilization. The need for several additional determinations or corrections has become apparent, as, for example, for the exchangeable tissue pools of glucose and ^{14}C-deoxyglucose. However, several possible modes of dealing with these problems are available, and it appears likely that the method will prove to be adequate after the solution of several technical but manageable problems. Such a method would be of enormous usefulness in studying cerebral energy metabolism in physiological, pharmacological, and pathological states.

Significance to Biomedical Research and the Program of the Institute. The vast majority of individuals with defective mental development (mental retardation, minimal cerebral dysfunction) are considered to have suffered some derangement of normal metabolic processes during the period of most rapid brain growth, i.e., just before and just after birth. Recent studies, both experimental and those involving children, confirm the evidence that there is a short period of brain growth when the demand for substrate for energy and growth is such that deficiencies result in irreversible deficit. The studies carried out in this laboratory are an effort to measure aspects of normal energy metabolism and the interdependence of these on the cerebral circulation. Our earlier work has shown that the developing cerebral vasculature responds by marked vasoconstriction when oxygen is present in excess. With the development of a method for measuring local glucose utilization, it is proposed to determine whether or not increases in oxygen tension in the blood may limit the supply of glucose, an essential substrate for brain growth and function. The outcome of such studies may have direct bearing on current medical practices in the care of the human newborn, especially the prematurely born, which are prone to sub-optimal mental development.

At the other end of the age spectrum, normal mental function is also known to be impaired by defective function of the cerebral circulation. The study of the effect of

diphenylhydantoin on cerebral blood flow is timely in the light of recent reports suggesting its administration leads to a reduction of episodes of cerebrovascular occlusion.

Proposed Course of Project: Major emphasis will be placed on the development of the method for measuring local cerebral glucose utilization and on the testing of the hypothesis that impairment of brain growth and development by high oxygen in the early postnatal period is the result of reduced cerebral blood flow and restricted glucose availability for nucleic acid synthesis.

Honors and Awards: None

Publications:

Kennedy, C., Grave, G. D., Jehle, J. W., and Sokoloff, L.: Blood flow to white matter during maturation of the brain. Neurology 20:613-618, 1970.

Sokoloff, L.: Neurophysiology and neurochemistry of coma. In Proceedings of the Second International Meeting of the International Society for Neurochemistry, Milan, Italy, September 1-5, 1969, to be published in a book entitled, "Hepatic Coma", by S. Karger (in press).

Kennedy, C., Grave, G. D., and Jehle, J. W.: The effect of hyperoxia on the cerebral circulation of the newborn puppy. Pediatric Research (in press).

Serial No. M-CM-DN-3
1. Laboratory of Cerebral Metabolism
2. Section on Developmental Neurochemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biochemical bases of alcohol addiction

Previous Serial Number: M-CS-CM-11

Principal Investigator: Louis Sokoloff, M.D.

Cooperating Units: Neil H. Raskin, M.D., Department of Neurology, University of California Medical Center, San Francisco, Calif.

Other Investigators: None

Man Years:

Total:	0.25
Professional:	0.25
Other:	0

Project Description:

Objectives: This project is directed at the acquisition of knowledge of the biochemical changes associated with chronic alcohol ingestion and the integration of such knowledge into a framework which it is hoped will provide a basis for the understanding of the mechanisms underlying alcohol addiction and the withdrawal effects.

Methods Employed: The enzymes associated with ethanol metabolism and that of its products will be assayed in brain, liver, and other tissues of normal rats and rats fed various amounts of ethanol for various periods. Evidence of enzyme inductions or repression by alcohol will thus be sought. Any changes in tissue enzyme levels will be examined for possible effects on the metabolism of other important metabolites on which these enzymes could conceivably act. In parallel studies purified enzymes of the alcohol metabolic pathway will be studied for substrate specificity and their effects on selected metabolites known to be important in the functional activity of the nervous system.

Classical methods of enzymology will be employed.

Major Findings: This project was actively worked on in this Section until June, 1968, when it was temporarily suspended because of the departure of Dr. Neil H. Raskin, a Research Associate in the Section, and the year's absence of the Section Chief, Dr. Louis Sokoloff, on a work assignment abroad. During the past year the project was reactivated on a collaborative basis with Dr. Raskin, who is presently an Assistant Professor in the Department of Neurology, University of California Medical Center, San Francisco, California. This project had previously demonstrated by means of a new assay technique the presence of alcohol dehydrogenase, the enzyme responsible for the metabolism of ethanol, in the brain. Previous efforts by other investigators to find the enzyme in brain had been unsuccessful because of inadequately sensitive and specific methods. The kinetic properties and the responsivity to specific inhibitors of the brain enzyme have been examined and compared to those of the liver enzyme and found to be almost identical. A tissue survey of the alcohol dehydrogenase has revealed its presence in all tissues which exhibit pathological changes with chronic excessive alcohol ingestion. In studies in rats it has found that the brain enzyme activity uses about 50% with chronic alcohol ingestion. This is in contrast to the liver enzyme which remains unchanged. This is the first evidence of a specific enzyme change in the brain with alcohol intake and suggests a possible relationship to the development of tolerance to ethanol and/or a biochemical basis for the development of CNS symptoms following withdrawal from alcohol after prolonged ingestion. Current studies are underway to determine if the enzyme change in brain is associated with behavioral changes.

Significance to Bio-medical Research and the Program of the Institute: Numerous drugs and chemical agents cause addiction which results in withdrawal symptoms when their use is discontinued. Alcohol is one of the most common. Although it is clear that some biochemical change must have occurred, none yet has been found which could satisfactorily explain the phenomenon. Elucidation of the biochemical mechanism of alcohol addiction might not only serve as a model for other types of addiction but might also lead to a more rational approach to therapy.

Proposed Course of Project: Studies will be continued to determine whether the changes in brain alcohol dehydrogenase activity with chronic alcohol intake are associated with pathological, biochemical and behavioral changes.

Honors and Awards: None

Publications:

Raskin, N. H., and Sokoloff, L.: Alcohol dehydrogenase activity in rat brain and liver. J. Neurochemistry 17: 1677-1687, 1970.

Raskin, N. H., and Sokoloff, L.: Ethanol-induced adaptation of alcohol dehydrogenase activity in rat brain. Science (in press).

Serial No. M-CM-MyC-1
1. Laboratory of Cerebral Metabolism
2. Section on Myelin Chemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biochemical studies on myelin and myelin basic protein

Previous Serial Number: Same

Principal Investigator: Russell E. Martenson

Other Investigators: Marian W. Kies and Gladys E. Deibler

Cooperating Units: None

Man Years:

Total:	3
Professional:	2
Others:	1

Project Description:

Objectives: To examine the relationships between structure and biological activity of the myelin basic proteins of several mammalian and nonmammalian species; to elucidate the phenomenon of charge heterogeneity of pure guinea pig myelin basic protein.

Methods Employed: (1) Polyacrylamide gel electrophoresis; (2) amino acid analysis of CNS proteins and their derivatives; (3) chromatographic fractionation of proteins and peptides; and (4) liquid scintillation techniques for detection of radioactivity.

Major Findings: (A) Microheterogeneity: Enzymatic alteration of total purified MyBP or its isolated components has been investigated to determine possible mechanisms for creation of different charge components in vivo. MyBP, like the histones, can be methylated by an enzyme present in the soluble supernatant fraction of brain homogenate, which transfers C^{14}-labeled methyl from S-adenosyl methionine to proteins. This reaction has been suggested as a possible source of heterogeneity by two investigators engaged in a study of MyBP structure. We have confirmed the observation that a soluble CNS fraction will methylate MyBP but we are unable to detect methylated derivatives in our purified preparations. Furthermore, we find that the introduction of methyl does not influence the pattern of heterogeneity;

therefore, it is unlikely that the reaction is contributing to heterogeneity in vivo.

(B) Identification of probable contaminants of purified myelin basic proteins: Although purified MyBP was originally believed to be homogeneous, we now know from immunochemical and electrophoretic data that highly antigenic contaminants accompany MyBPs through practically every purification step. One of these proteins is lysine-rich histone. We have recently isolated and identified this CNS histone in MyBP preparations. Two other proteins, one present also in liver, and the other a CNS-specific protein similar to BP in charge but larger in size, have been isolated. Recognition and removal of these contaminants is extremely important because of the potential use of MyBP for immunologic studies on cells and sera of neurologic patients.

(C) Species interrelationships: Last year we reported the isolation of two rat myelin basic proteins of different molecular size. We have now shown that mouse and hamster, members of the same rodent suborder as rats (Myomorpha), also have two MyBPs. Prairie dog, woodchuck, and squirrel (suborder Sciuromorpha) likewise have two myelin basic proteins. In contrast, a single MyBP was found to be characteristic of members of the third rodent suborder, Hystricomorpha--guinea pig and chinchilla.

(D) Relation of structure to biologic activity: By amino acid analysis and gel filtration we found that the two rat proteins differ from each other by about 40 amino acid residues. The composition of the larger rat protein is similar to bovine and human myelin basic proteins which have been sequenced by others. By comparing our analyses with the published sequences, we predicted the location and nature of the polypeptide segment which is present in the large rat MyBP molecule but absent in the small. Analysis of tryptic peptides and bioassay of the two proteins (large and small) have confirmed these predictions. Although the deletion does not prevent the small protein from functioning satisfactorily as a structural protein of myelin, it does markedly depress its encephalitogenic activity in guinea pigs but not in Lewis rats.

Significance to Biomedical Research and the Program of the Institute: Myelin basic protein is one of the best characterized proteins of the CNS, largely due to our efforts. Although its role in human autoimmune disease still remains to be defined, its use as an experimental tool is important because of the possibility that a peptide fragment or a modified MyBP might prove to be a useful protective antigen in humans. Our careful studies on protein purification along with our development of special analytical techniques have enabled us to resolve some of

the conflicting reports on the encephalitogenicity of MyBPs from various species. Guinea pigs, rats, monkeys, and rabbits have been used for bioassay with apparently inconsistent results. It is now evident that there are multiple encephalitogenic sites in these proteins which do not have equivalent activities in all species. Slight variations in structure have resulted in marked variations in activity.

Proposed Course of Project: In order for safe and effective treatment schedules to be developed the specific antigenic site which is involved in human demyelination must be identified just as it has been for different experimental animals. Furthermore, the nature of the biochemical lesion which is triggered by the immunologic event must be understood. We will continue to investigate the nature and cause of microheterogeneity since it is possible that the effectiveness of the basic protein in maintaining the normal structure of myelin is controlled through a mechanism which manipulates the charge on the molecule. Failure of this mechanism may be the initial biochemical lesion in demyelination.

Honors and Awards: None

Publications:

Martenson, R. E., Deibler, G. E., and Kies, M. W.: Rat myelin basic proteins: relationship between size differences and microheterogeneity. J. Neurochem. 17: 1329-1330, 1970.

Martenson, R. E., Deibler, G. E., and Kies, M. W.: Microheterogeneity and species-related differences among myelin basic proteins. Proc. Assoc. for Research in Nervous and Mental Diseases (in press).

Serial No. M-CM-MyC-2
1. Laboratory of Cerebral Metabolism
2. Section on Myelin Chemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Immunological studies on experimental allergic encephalomyelitis (EAE)

Previous Serial Number: Same

Principal Investigator: Marian W. Kies

Other Investigators: None

Cooperating Units: None

Man Years

Total:	2
Professional:	1
Others:	1

Project Description:

Objectives: Study of the roles of delayed (cellular) and immediate (humoral) hypersensitivity in the induction and prevention of autoimmune disease of the central nervous system.

Methods Employed: Induction of precipitating antibody in rabbits. Detection of antibody by immunoelectrophoresis and a new micro precipitin reaction developed for rapid survey of large numbers of antisera.

Major Findings: The preparation of quantities of anti-BP antibody is hampered by the susceptibility of rabbits to EAE. Other workers have used hapten-modified BP to depress the encephalitogenic activity and increase its antigenicity, but we feel that modified antigen would not yield antibody suitable for defining antigenic sites. Others have obtained antibody without inducing EAE by using (what we consider to be) prohibitive amounts of myelin basic protein (MyBP).

We have immunized 24 rabbits with varying amounts of either heterologous (guinea pig and human) or homologous (rabbit) MyBP. Antibody was produced readily in rabbits sensitized with GP-BP--as little as 1.4 mg in 3 weeks induced detectable antibody. A large amount of good antiserum has been obtained from a single

rabbit immunized repeatedly without succumbing to EAE (1-1/3 years after initial injection). Other rabbits immunized by similar injection schedules produced antibody but succumbed to EAE, 3 weeks, 2.5 months, and 6 months after initial immunization.

Homologous (R-BP) was much less antigenic (7 of 8 attempted immunizations were unsuccessful). One of these rabbits, however, was converted to an antibody producer by a single course of GP-BP injections following repeated injections with R-BP. The one rabbit which produced anti-RBP-antibody received only 1.4 mg R-BP but succumbed to EAE within 3 weeks of initial injection. Human MyBP was more antigenic than R-BP with about the same encephalitogenic activity as GP-BP.

In order to survey large numbers of sera, we developed a rapid qualitative test for antibody which requires minimal quantities of antigen and antisera:

MICRO-PRECIPITIN TEST

1. Mix 5 λ (5γ) BP + 50 λ antiserum; spot 5 λ on strips* saturated with pH 8.6 0.05 M Veronal,

or

1a. Saturate strips with BP in physiological saline, 0.1 mg/ml; spot 5 λ antiserum on blotted strips.

2. Store in humid chamber 1-3 hrs.

3. Immerse in physiological saline (4 x 30').

4. Stain with Amido black, rinse and air dry.

* Titan III cellulose acetate on mylar.

Good agreement was obtained between the new rapid method and the more precise but time-consuming demonstration of antibody by immunoelectrophoresis.

We are still unable to define the best way to induce antibody to MyBP but we believe our most effective schedule was an initial injection of 0.5 mg + 2.5 mg killed mycobacteria in oil:arlacel emulsion followed by a series of 9 injections of 0.5 mg BP in oil:arlacel (without mycobacteria) beginning one week after the first injection, 3 times weekly for 3 weeks.

Significance to Biomedical Research and the Program of the Institute: Participation of anti-BP-antibody in the pathogenesis of EAE, at least in guinea pigs, is doubtful: serum or humoral antibodies appear to have no pathogenetic effect in passive

transfer experiments; hardly any anti-BP-globulins can be detected during the induction or expression of active disease. Since the disease can be adoptively transferred by lymph node cells from sensitized donors to histocompatible recipients, it is possible that cell-bound antibodies play a role in pathogenesis.

Whether or not antibody is involved in pathogenesis in the rabbit is open to question. Nevertheless the study of antigenic structure can be facilitated by availability of good precipitating antibody for immunochemical analyses and this fact alone justifies our continued efforts to produce antibody in our study of this disease.

Proposed Course of Project: The new survey technique may prove to be useful for studies on human sera and will be examined critically with this in mind. The primary use of the rabbit antisera will be to assist us in structural studies of MyBP particularly with respect to cross-reactivity among MyBPs of various species.

Honors and Awards: None

Publications: None

Serial No. M-CM-MyC-3
1. Laboratory of Cerebral Metabolism
2. Section on Myelin Chemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: In vitro studies on delayed hypersensitivity

Previous Serial Number: Same

Principal Investigator: Marian W. Kies

Other Investigators: Bernard Driscoll

Cooperating Units: None

Man Years

Total:	3
Professional:	1
Others:	2

Project Description:

Objectives: To study the role of delayed hypersensitivity in the pathogenesis of EAE at the cellular level.

Methods Employed: Induction of EAE by adoptive transfer has been used as a tool to study mechanisms of suppression of EAE. Donor animals are sensitized with massive doses of homologous myelin basic protein (BP) and mycobacteria ($H_{37}R_v$). Suspensions of lymph node cells made on either day 5 or 12 post sensitization are injected intraperitoneally into normal, histocompatible recipients. Studies have been carried out on the effect of treatment of either cells or recipient on the success of the transfer.

Major Findings: It was reported earlier by members of this Section that guinea pigs made tolerant to EAE by either pre-immunization with moderate amounts of myelin BP alone or by mycobacteria alone fail to display either clinical or histological signs of EAE when subsequently challenged with an encephalitogenic emulsion (i.e., MyBP plus mycobacteria). Neither can these tolerant animals be passively sensitized by adoptive transfer of lymph node cells from sensitized donors.

Reports on recent experiments with other antigens have led to hypotheses concerning specific cell-to-cell interactions and the necessity for at least two distinct cell populations in the

mediation of both humoral (immediate) and cellular (delayed) responses. We have underway a series of experiments to explore the validity of these hypotheses concerning cell-to-cell interactions in EAE. Two basic approaches are being used: attempts to break tolerance by the synergistic effects of single or mixed cell populations on active induction; and the possibility of synergy between cell populations in successful adoptive transfer of EAE.

Currently, tolerant animals are being given transfers of various normal cells (lymph node, spleen, thymus, or peripheral leucocytes) at the time they are re-challenged with encephalitogen in Freund's adjuvant. If we are able to break tolerance by this method, we hope to identify the cell population which is capable of restoring immunologic competence. Another experiment underway is to transfer various normal cell populations simultaneously with sensitized lymph node cells to tolerant animals. If either technique is successful we will be able to attack the problem of desensitization of human patients in a more rational manner than has heretofore been possible.

We are attempting to identify the "effector" cell in EAE. Lymph node cells are isolated from sensitized guinea pigs in order to study their binding affinity for I^{125}-BP. Mild fixation has been utilized prior to binding studies in order to prevent metabolic activity from interfering with the binding assay. Continuous production and liberation of specific membrane proteins into the culture medium might prevent a stable reaction with I^{125}-BP.

To date several different methods of cell preparation (live as well as fixed cells), antigen presentation to the "sensitized" cells (soluble as well as particle-bound antigen), and final separation of sensitized cell-antigen complexes have been used. The results obtained are encouraging, indicating a range of 2-10 fold more binding of antigen by cells from sensitized animals than by cells from control animals. This success led to an experiment designed to indicate antigen-antibody type specificity in this binding, much like the typical precipitin curves obtained with serum antibody. To a constant number of either sensitized or control cells gradually increasing amounts of antigen were added. The results indicate a zone of steep linear increase in antigen binding to sensitized cells followed by an extended region with no further antigen binding (plateau region). No matter how much antigen was added no increase in binding could be observed. In contrast, the control cells displayed a shallow, linear increase in background binding.

Despite these successes, we are still searching for more reproducible assay conditions. Some cell preparations yield

good results, while others show only a slight increment of binding over that of control cells. This could possibly be a real phenomenon characteristic of the process of DH and not a technical failure. Assay of a larger number of animals at various times during the course of EAE by several methods will help to clarify this situation.

Significance to Biomedical Research and the Program of the Institute: Several neurologic diseases are thought to be autoimmune in nature although most investigations have failed to provide convincing evidence of cytotoxic antibodies in humans with these diseases. The current hypothesis is that sensitized cells rather than antibodies are responsible for CNS damage. Study of adoptive transfer of an experimental autoimmune disease (EAE) permits the separation of cellular sensitization (in the donor) from the mechanism of lesion formation (in the recipient). In the two most closely related human diseases (acute disseminated encephalomyelitis or idiopathic polyneuritis) the initial sensitization processes remain a complete mystery but the evidence continues to accumulate in favor of the participation of sensitized cells in the development of the CNS or PNS lesions. Thus treatment of the latter stage of adoptive transfer (development of CNS lesions in the recipient) can be used as a model for treatment of human disease.

Proposed Course of Project: In the field of CNS autoimmunity, knowledge of structure of the encephalitogen has far surpassed our understanding of the role of cellular sensitivity in pathogenesis. Although we are able to define encephalitogenic sites the information tells us nothing of the details of the disease process. In essence, the experimental disease consists of the production of myelin BP sensitized cells which damage the target organ because of some specific reaction with intrinsic antigen. Lesion formation, however, also depends on the participation of normal cells in a manner which has not yet been defined. We intend to continue our search for "helper" cells and will attempt to define the nature of their interaction with "effector" cells. Continuation of our study of the nature of the binding site on the lymphocyte membrane of "effector" cells is also part of our current plans.

Honors and Awards: None

Publications:

Alvord, E. C., Jr., Shaw, C.-M., Lisak, R. P., Falk, G. A., and Kies, M. W.: Relationships between antibodies and experimental allergic encephalomyelitis. V. Antibodies and delayed hypersensitivity in production and prevention of experimental allergic encephalomyelitis. Int. Arch. Allergy 38: 403-412, 1970.

Lessell, S., Behan, P., Lamarche, J., and Kies, M.: Sensitivity to encephalitogenic protein in optic neuritis. Brit. J. Ophthal. 54: 731-735, 1970.

Levine, S. Hoenig, E. M., and Kies, M. W.: Allergic encephalomyelitis: immunologically specific inhibition of cellular passive transfer by encephalitogenic basic protein. Clin. Exp. Immun. 6: 503-517, 1970.

Lisak, R. P., Falk, G. A., Heinze, R. G., Kies, M. W., and Alvord, E. C., Jr.: Dissociation of antibody production and disease suppression in the inhibition of allergic encephalomyelitis by myelin basic protein. J. Immun. 104: 1435-1446, 1970.

Rocklin, R. E., Sheremata, W. A., Feldman, R. G., Kies, M. W., and David, J. R.: The Guillain-Barre syndrome and multiple sclerosis. New Eng. J. Med. 284: 803-808, 1971.

Serial No. M-CM-MeC-1
1. Laboratory of Cerebral Metabolism
2. Section on Membrane Chemistry
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Study of the modulation of central nervous system metabolism and function through alterations in membrane permeability and transport

Previous Serial Number: Same

Principal Investigator: Harry R. Steinberg, M.D.

Other Investigators: Ana Maria Lennon, Ph.D., James D. Brown, Carolyn S. Cottingham, Louis Sokoloff, M.D., and Jack Durell, M.D., Consultant, The Psychiatric Institute, Washington, D.C.

Cooperating Units: None

Man Years:

Total:	3.5
Professional:	1.5
Other:	2.0

Project Description:

Objectives: Previous investigation in this laboratory, as well as studies of others, indicates that the alteration of membrane properties may play a central role in the modulation of central nervous system (CNS) activities. The objective of this study is to define the mechanisms by which CNS membranes may be altered and to relate these changes to those caused physiologically, by putative neurotransmitters.

Methods Employed: This problem has been approached at three levels of complexity. At the highest level, intact cells in an isolated tissue have been studied while maintaining many of their usual intercellular relations. At the next level, tissue homogenates have been fractionated so that specific portions of the cells may be subjected, in vitro, to the action of various hormones and pharmacological agents, to demonstrate

their action on these subcellular components in the absence of the remainder of the cell. Finally the action of these agents is observed in simpler systems containing partially purified macromolecules to provide further insight into the mechanism of action. At all levels, alterations in the membrane constituents, their interaction with active transmitters and changes in permeability are of particular interest. High voltage electrophoresis, column and thin-layer chromatography, differential and density gradient centrifugation, and studies of the turn-over of radioactively labelled compounds represent a major portion of the methodology.

Major Findings: A number of studies have suggested that the enhanced labeling of phosphatidylinositol which is observed when ACh and eserine are added to various preparations of neural tissue is coupled to the combination of ACh with its receptor. We have attempted to extend these observations to chronically denervated rat hemidiaphragm in which preparation there is a spread of ACh sensitivity over the entire muscle cell surface. No effect on incorporation of radioactive inorganic orthophosphate into phosphatidylinositol was caused by addition of ACh and eserine either to chronically denervated (7 days) acutely denervated (24 hours) or normal hemidiaphragm, with either 2-minute or 30-minute periods of incubation. Under some experimental conditions acutely denervated hemidiaphragm shows an increased incorporation of radiophosphate into phosphatidylinositol relative to phosphatidylcholine.

Also, in an attempt to better understand the significance of the ACh-stimulated increase in incorporation of radiophosphate into phosphatidylinositol, the laboratory initiated studies designed to clarify the role of polyphosphinositides in certain membrane functions. This work has included a study comparing the effect of single contractions of frog rectus muscle on the pool size of muscle phosphoinositide as well as attempts to demonstrate various enzymes of phosphoinositide metabolism in muscle microsomes. As yet, no definite conclusion concerning the role of phosphoinositide in muscle Ca^{++} metabolism can be drawn from these experiments though preliminary results suggest that such a role exists.

Significance to Bio-medical Research and the Program of the Institute: The mechanism by which neurotransmitters exert effects on post-synaptic and effector cells is at present unknown. Elucidation of this mechanism would very probably shed considerable light on the mechanism of action of many psychotropic drugs. Further, since many hallucinogenic drugs are related chemically to neurotransmitters, elucidation of the mechanism of transmitter effect would very likely greatly

increase understanding of induced hallucinations and perhaps naturally occurring hallucinations as well. There is, in addition, a great theoretical interest in the problem of how transmitters cause post-synaptic and effector cell membranes to alter in permeability.

Proposed Course of Project: Further studies of phosphoinositide metabolism and the metabolism of other phospholipids in skeletal muscle and nervous tissues are planned, as well as continued efforts to improve the reliability of results in the synaptosome preparation so as to allow further pharmacological investigation.

Honors and Awards: None

Publications:

Steinberg, H. R., and Durell, J.: Effects of denervation on the incorporation of ^{32}P into phosphatidyl inositol and other phospholipids of rat diaphragm. J. Neurochemistry 18:277-286, 1971.

Serial No. M - LGCB 16B
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Amino Acid tRNA Synthetases. Their Role In Protein Synthesis, and Interaction With tRNA

Previous Serial Number: M-LGCB 16 and 16A

Principal Investigators: G. L. Cantoni

Other Investigators: Elizabeth A. Boeker

Cooperating Units: None

Man Years

Total: 1-1/4
Professional: 1-1/4
Other: 0

Project Description:

Objectives: Aminoacyl tRNA synthetases catalyze the first reaction of protein synthesis:

$$\text{Amino acid} + \text{ATP} + \text{Synthetase} \rightleftarrows \text{Aminoacyl-AMP-Synthetase} + \text{P}\sim\text{P}$$

$$\text{Aminoacyl-AMP-Synthetase} + \text{tRNA} \rightleftarrows \text{Aminoacyl-tRNA} + \text{AMP} + \text{Synthetase}$$

$$\text{Amino acid} + \text{ATP} + \text{tRNA} \overset{\text{Synthetase}}{\rightleftarrows} \text{Aminoacyl-tRNA} + \text{AMP} + \text{P}\sim\text{P}$$

In bacteria there are 20 synthetases, one for each amino acid. In eukaryotic cells, however, multiple synthetases acting on the same amino acid have been shown to exist. These redundant synthetases have different subcellular localizations, in the cytoplasm, the mitochondria, or the nuclei, and frequently have different catalytic and structural properties.

The specificity of the translation of genetic information from DNA into linear polypeptide chains depends critically on the recognition by aminoacyl tRNA synthetases of their specific amino acids and cognate tRNA molecules. Although each tRNA has a unique base sequence, the secondary and tertiary structures of these nucleic acids are all rather similar, and the mechanism by which a specific synthetase recognizes the correct tRNA is not known. The specificity of this recognition cannot reside in the anti-codon unique to each tRNA since, in several cases, a single synthetase recognizes multiple tRNA's, all coding for the same amino acid but having different anti-codons. The interaction between tRNA and aminoacyl tRNA synthetases thus provides an ideal system for investigation of the mechanism by which proteins recognize nucleic acids, a mechanism central to a variety of problems of great biological importance.

The aminoacyl tRNA synthetases also represent a family of enzymes which catalyze formally similar reactions with different substrate specificities. A class of enzymes such as this might be expected to show rather similar structural parameters, but simple structural analysis has already shown that this is not the case. Based on the available date for the molecular weight and subunit structure of less than half of the 20 synthetases, at least three classes are distinguishable: monomers with a molecular weight of approximately 100,000, dimers with a total molecular weight also approximating 100,000, and tetramers with a total molecular weight around 180,000. The data currently available are not sufficient to interpret these differences meaningfully, and a great deal of additional information will be required to achieve an adequate understanding.

Methods Employed: Amino acid activation can be measured either by the incorporation of ^{32}P~P into ATP or the incorporation of ^{14}C-serine into tRNA. Classical methods of enzymology and protein chemistry are used in the purification and structural characterization of the synthetase. In a particularly useful feature of this system, both the aminoacyl-AMP-synthetase complex, formed in the absence of tRNA, and the synthetase-tRNA complex, formed in the absence of ATP and serine, can be isolated by gel filtration or trapped on nitrocellulose filters, allowing independent evaluation of the characteristics of each interaction. The information thus obtained using substrate levels of enzyme complements that obtained from kinetic analyses using catalytic quantities of the synthetase.

Major Findings: The serine tRNA synthetase of E. coli B has been purified to homogeneity; the procedure is adequate for the isolation of sufficient enzyme to carry out structural studies. The enzyme is essentially homogeneous by the criteria of acrylamide gel electrophoresis and isoelectric focusing.

A preliminary estimate of the molecular weight of the native enzyme of 90,000 was obtained by equilibrium ultracentrifugation. The enzyme, however, shows a tendency to dissociate into subunits under these conditions and considerably more work will be required to establish the molecular weight of the native enzyme with certainty. The enzyme appears to be composed of two polypeptide subunits; the molecular weight of these, as determined by acrylamide gel electrophoresis in sodium dodecyl sulfate, is 53,000 $\pm$ 3000. Under denaturing conditions, these subunits show no detectable heterogeneity with regard to either size or charge.

Equilibrium dialysis of the synthetase and ATP, in the absence of serine and tRNA, gives a stoichiometry of one mole of ATP per 53,000 g of enzyme and an ATP binding constant of $4.4 \times 10^4\ M^{-1}$. Measurement of the formation of the seryl-AMP-synthetase complex in the absence of tRNA, using gel filtration under steady state conditions, shows that, at saturation, one mole of complex is formed per 53,000 g. The serine tRNA synthetase, therefore, consists of two apparently identical subunits, each having a molecular weight of 53,000 and one active site.

Scientific Significance: Interaction between nucleic acids and proteins is an important biological phenomenon. The interaction of an amino acid tRNA synthetase with the corresponding tRNA in a highly purified system may afford a useful model for such interactions in general. In addition, this study should provide important information about the complex two-step reaction catalyzed by the amino acid tRNA synthetases.

Proposed Course of Research: These studies will be continued as they are part of the Laboratory's long-range program on the nucleic acid protein recognition and interactions.

Honors and Awards: None

Publications: None

Serial No. M - LGCB 18
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies on the Structure and Function of Thetin-Homocysteine Methylpherase and Lactose Synthetase

Previous Serial Number: Same

Principal Investigator: Werner A. Klee

Other Investigators: Claude B. Klee

Cooperating Units: Laboratory of Biochemical Pharmacology, NIAMD

Man Years

Total: 1
Professional: 1/2
Other: 1/2

Project Description:

Objectives: Macromolecular complexes on many levels are clearly a central principle of biological organization. This project is aimed at learning how the properties of such complexes can differ from those of the isolated components in two enzyme systems. One enzyme, thetin-homocysteine methylpherase, exhibits a number of interactions of like protein species; the other, lactose synthetase, is an example of an enzyme in which two very different protein species interact to form the whole.

Methods Employed: We are using the standard method of protein chemistry including chromatography, electrophoresis, preparative and analytical ultracentrifugation spectrophotometry and spectropolarimetry. In addition, many of the standard analytical techniques of enzymology are being employed. Band sedimentation methods for studying macromolecular interactions are being developed as part of this project.

Major Findings: Lactose synthetase was known to consist of two protein componants both of which are found in lactating mammary glands and in milk. The two proteins are the A-protein and α-lactalbumin. The latter is a well known low molecular weight milk protein. We have isolated the A-protein from milk and shown it to be a mixture of closely related glycoproteins which are of similar size and enzymatic activity. The A-protein alone can carry out galactose transfer reactions from UDP-galactose to a variety of glycoproteins, glycolipids and to some simple sugars such as N-acetylglucosamine. Although it had at first been believed that the A-protein will not transfer galactose to glucose (to make lactose) in the absence of α-lactalbumin we, and others, have found that at very high glucose concentrations α-lactalbumin is not required. The effect of α-lactalbumin on the system is to produce a dramatic increase in the affinity for sugar acceptors be they glucose or N-acetylglucosamine. This simple picture is complicated by the existence of a substrate inhibition seen at high concentrations of acceptor sugars. α-lactalbumin enhances this effect as well and so is seen to stimulate or inhibit glycosyl bond formation depending on the acceptor sugar concentration.

These kinetic observations made it appear highly likely that α-lactalbumin functions by combining with the A-protein to form a multisubunit complex. We have found that such complexes are indeed formed but only in the presence of one of the substrates of the enzyme, either UDP-galactose or N-acetylglucosamine. The latter sugar is much more effective than glucose by virtue of its greater binding affinity. Complex formation was demonstrated by a number of methods including a newly developed modification of band sedimentation in the analytical ultracentrifuge. The complex contains one molecule of A-protein and one molecule of α-lactalbumin and is quite easily dissociated. Although α-lactalbumin is the only protein known to function in this system, it has been found that the only modifications to its structure which will prevent interaction with the A-protein are major ones such as disulfide bond reduction or extensive proteolysis. Modification of amino acid residues such as tyrosine, methionine, histidine and at least some aspartic and glutamic acids results in only a minor decrease in activity. Thus, the interaction of the two proteins may involve the mutual recognition of large areas of their surfaces.

Scientific Significance: The two enzymes under study are both important to the economy of mammals. Thus, thetin-homocysteine methylpherase plays a major role in methyl group metabolism and lactose synthetase is responsible for

the synthesis of lactose, one of the main sources of energy of newborn mammals. The lactose synthetase system represents a novel type of evolutionary adaptation in which an enzyme which is normally used for glycoprotein and glycolipid biosynthesis (the A-protein) is modified to accomplish a new function, lactose biosynthesis, by complexing with another, non-catalytic protein, α-lactalbumin. Thus, the system is a clear example of how protein function can be modified in a dramatic way by incorporation into a more complex structure.

Proposed Course of Research: We propose to continue our studies of the mode of formation and properties of macromolecular complexes. Since the A-protein is very widely distributed as a membrane bound enzyme we hope to be able to extend our work to even higher levels of structural organization.

Honors and Awards: None

Publications:

Klee, W.A., and Klee, C.B.: The role of α-lactalbumin in lactose synthetase. Biochim. Biophys. Res. Commun. 39: 833-841, 1970.

Serial No. M - LGCB 26A
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Purification of Serine tRNA from E. coli and Determination of Its Base Sequence

Previous Serial Number: M-LGCB 34 and M-LGCB 26

Principal Investigator: H. Maruyama

Other Investigators: H. H. Richards

Man Years

Total: 1
Professional: 1/2
Other: 1/2

Project Description:

Objectives: Knowledge of the nucleotide sequence of an amino acid specific tRNA is a necessary prerequisite to understanding the means by which the tRNA performs its vital intracellular role in protein synthesis. Comparison of the structures of tRNAs from different organisms each specific for the same amino acid will further aid in our understanding of the mechanism of function of these molecules.

Methods Employed: Purification of serine tRNA from E. coli by column chromatography in three systems; benzoylated DEAE cellulose, hydroxyapatite chromatography on the aminoacylated derivative of serine tRNA, and finally chromatography of the non-acylated serine tRNA. Purified $tRNA^{Ser}$ is then cleaved into smaller fragments by the action of specific nucleases and these fragments are analyzed by further enzymatic degradation. Work is presently being undertaken to determine the sequence of two of the serine specific tRNAs from E. coli. The methods employed for sequencing ribonucleic acids are constantly being improved. We have utilized the enzyme polynucleotide kinase to label the 5' terminus of fragments obtained by specific nucleolytic cleavage. New techniques for isolation and characterization of the oligonucleotide fragments are being explored and developed.

Major Findings and Scientific Significance: Analysis of the oligonucleotide labeled fragments from E. coli serine tRNA reveals large differences from the fragments obtained from yeast serine tRNA. This is of great interest since the tRNA synthetase from yeast will recognize the tRNA from E. coli. An imaginative comparison of the primary sequence of the serine tRNA from E. coli and yeast may reveal the so-called "recognition" area in the structure of the tRNA molecule. We are in the process of determining whether enough sequence data has been obtained to permit the description of the primary sequence of serine tRNA from E. coli.

Proposed Course of Research: Further work is not contemplated at the present time due to inadequate manpower.

Honors and Awards: None

Publications: None

Serial No. M - LGCB 35
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies on Protein Conformation and Limited Proteolysis

Previous Serial Number: Same

Principal Investigator: Werner A. Klee

Other Investigators: None

Cooperating Units: None

Man Years

Total: 1
Professional: 1/2
Other: 1/2

Project Description:

Objectives: Although it is now a well established principle that the linear sequence of the amino acids of a polypeptide chain determines the nature of the characteristic structure (conformation) of proteins, the process whereby this transformation of two dimensional information to a three dimensional structure occurs is not well understood. The ultimate goal of this project is to supply experimental data which may lead to some insight into this problem. A closely related question which we would like to help answer is: What is the nature of the conformational changes which take place in protein systems and what is the role of such structural flexibility in the functioning of macromolecular systems?

Methods Employed: One way of finding out something of the nature of the conformational determinants of proteins is to study the properties of smaller fragments of the molecules. We have prepared a number of peptides of overlapping sequence from two proteins by a combination of proteolytic and chemical cleavage, and are studying the conformational properties of these materials by physical methods which include spectropolarimetry, ultraviolet and nuclear magnetic spectroscopy, ultracentrifugation and titrimetry. These studies are performed over a range of solvent conditions and temperatures

and provide information on the conformation of these peptides in solution which can then be compared with the known structures of these materials when they are part of the intact protein in the crystalline state. We also study the nature of the conformational changes in which intact proteins participate on variation of the state of their environment or as a result of interactions with other kinds of molecules. This work uses the same kinds of physical methods described above in conjunction with some more subtle probes of structure such as limited proteolytic cleavage of exposed (and unstructured) regions.

Major Findings: We have studied in detail the conformational properties of a number of peptide fragments of ribonuclease and of insulin. The peptides chosen for study to date are all fragments containing the amino terminus of the protein and vary simply in the length of the rest of the polypeptide chain which remains attached. In this way a comparison of the properties of closely related peptides gives information about the structure determining role of successive regions of the polypeptide sequence. The results of this work to date are consistent with the hypothesis that those portions of the polypeptide chain of the two proteins which are found to be in a helical region of the intact protein participate in a helix-like structure in solution as well. In isolation, these helices have rather different stability properties from those of the protein and may be more appropriately considered to be "nascent" helices rather than fully formed ones. Peptide segments which do not participate in a repeating structure in the intact protein appear to be essentially disordered in solution. An analysis of the published data from other laboratories with peptides derived from other proteins indicates that the phenomenon of "nascent helix" formation by fragments of helical regions of intact proteins may be a general one.

Our work with ribonuclease fragments had shown that the nascent helix near the amino-terminus of the molecule is stable only at low temperatures when fragments of short length are studied. The behavior of the nascent helix of the insulin B chain, (which corresponds to the amino terminus of proinsulin) is interesting in that it is stable only at high temperatures (37°) and becomes disordered as the temperature is lowered. It thus appears that there may be more than one kind of nascent helix which is formed. It may be that the structure in the case of the insulin fragment is stabilized largely by hydrophobic interactions whereas that of the ribonuclease fragment is stabilized primarily by other kinds of forces.

Scientific Significance: These studies are providing a stock of techniques which may be generally useful in studying the nature of the determinants of protein structure. On the basis of our results it would appear that short range interactions, among near neighbor amino acid residues, control the nature of the protein structure to an important degree. The specific types of short range interactions involved are yet to be determined but it would appear that there may be at least two distinct ways of specifying helical structures.

Proposed Course of Research: We intend to continue these studies along the general lines discussed above.

Honors and Awards: None

Publications:

Brown, J.E., and Klee, W.A.: The helix-coil transition of the isolated amino terminus of ribonuclease. Biochemistry 10: 470-476, 1971.

Serial No. M - LGCB 56
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Determination of the Effect of Small Viruses and Their Nucleic Acids On the Biochemistry of Living Organisms

Previous Serial Number: Same

Principal Investigator: Carl R. Merril

Other Investigators: M. Gottesman, H. Nash, J. Petricciani and M. Geier

Cooperating Units: Laboratory of Neurochemistry, NIMH; Laboratory of Molecular Biology, NIAMD; Pathology Laboratory, Division of Biologics Standards, NIH, Institute of Cancer Research, Columbia University

Man Years

Total: 2
Professional: 1
Other: 1

Project Description:

Objectives: An attempt to determine the genetic information contained within the nucleic acids of small viruses and its effect on various organisms.

Methods Employed: Biochemical techniques for purification and analysis of small viruses and nucleic acids, ultraviolet spectroscopy, density gradient ultracentrifugation, bacteriophage genetics, radioactive tracer techniques and mammalian tissue culture methods.

Major Findings: 1. In viruses which are capable of integrating into a host chromosome, such as λ bacteriophage, a repressor molecule is produced which prevents expression of other phase functions. Repressor synthesis is itself under positive control. The initiation of the expression of the repressor gene requires CII and CIII gene products,

or the presence of the repressor molecule itself. The ability of the repressor to promote the initiation of repressor synthesis suggested that the repressor molecule might influence its own rate of synthesis. To test this we examined the rate of repressor transcription, the level of immunity and the amount of repressor in lysogens bearing one, two or three viruses. We found that the rate of repressor gene expression is independent of repressor concentration and conclude that the intracellular concentration of repressor is not a limiting factor in the rate of repressor synthesis. This study was conducted in collaboration with Dr. Max Gottesman and involved analytic and preparative ultracentrifugation of virus and their nucleic acids, radioactive tracer techniques, and genetic analysis of bacteria and viruses.

2. A transducing bacteriophage, λpGal, was inoculated into human cell cultures derived from a patient with galactosemia and caused increased $C^{14}O_2$ production from galactose-1-C^{14} as compared with controls. The per cent of conversion of galactose to CO_2 was similar in parallel experiments using human and bacterial cell cultures. A direct assay for transferase (the enzyme which is missing in galactosemia) was positive in the human galactosemic cells exposed to λpGal and suggested that a bacteria gene can be introduced into human cells through a transducing phage and retain biological activity.

Scientific Significance: 1. The total amount of λ virus specific transcription in lysogens directly reflects their prophage content. Thus, a single lysogen has half as much message as a double and one-third as much as the triple lysogen. A surprising feature of this transcription is that a large portion of the transcription derives from regions of the virus other than the repressor gene, however, the amount of repressor message was shown to reflect the number of prophage copies. Because of the long hybridization times required for its annealing, we assume that the non-repressor message is composed of low concentrations of many different messenger species. The development of techniques to follow specific genetic messages may prove important in future studies of genetic diseases and viral infections.

2. It is not known at the present time whether the transferase production is the result of integration of the viral DNA into the host genome or whether the viral DNA is functioning independently in the cytoplasm in a plasmid like fashion, or, in some totally unknown manner. However, the results presented here suggest that it might be possible

to introduce a selected bacterial gene into human cells *in vitro*, using phage as a vehicle. Our results are also in agreement with recent evidence that there are much greater biochemical similarities between far-ranging living species than had been appreciated previously.

Proposed Course of Research: The study of the functions of the small viruses and their nucleic acids will be extended from bacteria to more complex systems such as the galactosemic human cell cultures with emphasis on molecular level effects.

Honors and Awards: None

Publications:

Merril, C.R., and Geier, M. The effect of freezing and DEAE-D in spheroplast assays. *Virology* 42: 780-782, 1970.

Serial No. M - LGCB 57
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Studies on the Origin and Function of Dihydrouridine Residues in tRNA

Previous Serial Number: Same

Principal Investigator: H. Maruyama

Other Investigators: H.H. Richards

Cooperating Units: None

Man Years

Total: 1
Professional: 1/2
Other: 1/2

Project Description:

Objectives and Background: Transfer RNA contains a variety of minor nucleotides. Among these, dihydrouridine is of interest because its location in the primary base sequence occurs only at positions 16-20 from the 5' phosphate terminus. It is of interest to note that in bacterial tRNA these positions are generally occupied by cytidine residues. This observation suggests that cytidine, rather than uracil, is the more immediate precursor of dihydrouridine, perhaps via dihydrocytidine, a compound known to undergo spontaneous deamination to dihydrouridine.

Methods Employed: The determination of dihydrouridine is based on a change in its UV absorption spectrum upon exposure to alkali. Although the sensitivity of this method is not very great (10 μMoles/cc) the method is rapid and convenient and can be used to screen yeast extracts for the presence of an enzyme capable of generating dihydrouridine in E. coli tRNA. Yeast was chosen as a source of the enzyme because as noted above, yeast tRNA regularly contains dihydrouridine whereas E. coli tRNA was chosen as substrate since it does not contain dihydrouridine.

Results: Preliminary results indicate that yeast extracts and ammonium sulfate fractions derived from them were capable of generating dihydrouridine-like compounds using E. coli tRNA as substrate. However, in contrast to expectation yeast tRNA also seemed to serve as substrate. Further work using two different methods for the identification of dihydrouridine as the reaction product have given variable and ambiguous results. Efforts at enzyme purification have likewise failed. We are not yet in a position to move ahead with confidence and further experimentation will be required to ascertain whether, in fact, the reaction we are interested in can be detected and usefully studied in the system we have devised.

Scientific Significance and Proposed Course of Research: This work is part of a long-range study on the molecular biology of tRNA and on its biosynthesis.

Honors and Awards: None

Publications: None

Serial No. M - LGCB 58
1. Laboratory of General and Comparative Biochemistry
2. Section on Proteins
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Ribonuclease Specific for RNA-DNA Hybrids

Previous Serial Number: None

Principal Investigator: G. L. Cantoni

Other Investigators: Roy C. Haberkern

Cooperating Units: None

Man Years:

Total: 1-1/2
Professional: 1-1/2
Other: 0

Project Description:

Objectives: Recent description of RNA-dependent DNA polymerase enzymatic activity in RNA tumor viruses, and the viruses' known requirement for DNA synthesis for their replication suggest the importance of RNA-DNA hybrid molecules to viral metabolism.

A partially purified enzyme has been described from calf thymus which appears to catalyze hydrolysis of the RNA moiety of an RNA-DNA hybrid polynucleotide. The enzyme is reported to be inactive with single or double stranded RNA as substrate. Further purification and characterization of this enzyme have been undertaken.

Methods and Findings: The ribonuclease has been purified beyond the degree reported in the literature by standard preparative procedures. It is assayed using labelled RNA-DNA hybrids synthesized with E. coli RNA polymerase also prepared in this laboratory. To date the enzyme has been purified in excess of 100-fold and continues to demonstrate a requirement for RNA in the hybrid form as substrate.

Scientific Significance: RNA tumor viruses are not presently available in sufficient quantities to make feasible isolation of the enzymes necessary for their replication. To date

studies of these processes are limited to pharmacologic interference with the constituitive reactions of the replicative cycle, and these agents are of as yet uncertain specificity and mode of action. Disruption of the hybrid molecule with an enzyme of known specificity and mechanism would be an important adjunct to the study of viral replication and cell transformation, until such time as direct investigation of these enzymatic reactions is possible.

Proposed Course of Research: Further purification and characterization of the ribonuclease and its effect on replicating virus are in progress.

Honors and Awards: None

Publications: None

Serial No. M - LGCB 43
1. Laboratory of General and Comparative Biochemistry
2. Section on Alkaloid Biosynthesis
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Homocystinuria: Methionine Metabolism in Mammals

Previous Serial Number: M - CP 43

Principal Investigator: S. Harvey Mudd, M.D.

Other Investigators: R. W. Uhlendorf, Ph.D.

Cooperating Units: Laboratory of Viral Immunology, DBS

Man Years:

Total: 2
Professional: 1
Other: 1

Project Description:

Objectives: The objectives of this project are to obtain a detailed knowledge of the biochemistry of sulfur-containing compounds in the mammalian body, with emphasis on the transsulfuration pathway. Special attention will be focused on the regulatory devices which control this area of metabolism.

Methods Employed: The methods employed have been presented in detail in previous Annual Reports. In general, standard methods of enzyme purification and assay have been employed. Automated amino acid analysis has been used extensively. The techniques used for growth of cells in tissue culture are the usual ones. Attempts are currently underway to produce vitamin B_{12}-limited media by replacement of the protein of the usual medium with protein derived from B_{12} deficient animals. Alternatively studies of cells which may possibly grow in the absence of protein will be undertaken.

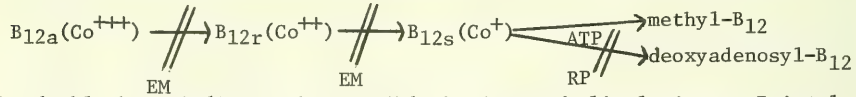
Major Findings: (a) Investigations of mammalian B_{12} metabolism have been continued. This work follows from the study of a child, E.M., described in detail in the previous annual report, who was demonstrated to have deficient activities of the two enzymes known in mammals to depend upon B_{12} derivatives for their activity. Our working hypothesis is that this child was blocked in an early step of B_{12} metabolism with the result he was unable to convert vitamin forms of B_{12} to coenzymatically active forms.

The expected result would be deficient activity of both the B_{12}-dependent enzymes.

Recently, Dr. Stephen Goodman of the Univ. of Colorado discovered a pair of siblings who have both homocystinuria and methylmalonia aciduria, the hallmark biochemical abnormalities in E.M. In collaboration with Dr. William Uhlendorf, Division of Biologic Standards, and Dr. Goodman, fibroblasts grown from these patients in tissue culture have been studied. The evidence suggests they have a lesion similar to that in E.M. Specifically, their homocystinuria is due to a deficient activity of N^5-methyltetrahydrofolate-homocysteine methyltransferase which, in turn, is due to a lack of the cofactor for this reaction, methyl-B_{12}. Our studies suggested also that these patients might respond clinically to massive doses of hydroxy-B_{12}. Such a response has now been documented. Further studies will relate the chemical form and the dose of B_{12} to the therapeutic response. Understanding of these factors may be expected not only to be useful for management of patients with this and related diseases, but to furnish insight into the mammalian metabolism of B_{12}.

In a second collaborative project, we have investigated homocysteine metabolism in the cells of a patient, first described by Dr. Leon Rosenberg, Yale University. This patient has methylmalonic aciduria which responds to very large doses of hydroxy-or cyano-B_{12}, in this respect resembling the patients described above. He differs by having no homocystinuria. We have now shown that the cells of this patient have normal N^5-methyltetrahydrofolate methyltransferase activity and that the distribution of this enzyme between apoenzyme and holoenzyme is normal. Studies of the ability of the cells of this patient, R.P., and of cells of E.M. to accumulate B_{12} derivatives formed from ^{57}Co-hydroxy-B_{12} have been performed. Cells of E.M. accumulate neither methyl-B_{12} nor deoxyadenosyl-B_{12}. Cells of R.P. accumulate methyl-B_{12}, but not deoxyadenosyl-B_{12}. This completes the demonstration that each of these patients has abnormal B_{12} metabolism and that the two defects differ from one another.

All available evidence is compatible with the following scheme:



The double bars indicate the possible basic metabolic lesions. Initial attempts to directly test this hypothesis, carried out in collaboration with Dr. Abeles have yielded no clear answers. The experimental system is a difficult one and we hope to continue these efforts.

(b) Studies of cystathionine synthase deficiency have been continued. This condition accounts for most known cases of homocystinuria. We have over several years accumulated 30-40 fibroblast lines which are deficient in cystathionine synthase. These cells offer favorable experimental material for the study of various aspects of the molecular biology of

cystathionine synthase deficiency. The assay for cystathionine synthase activity has now been made sensitive enough to quantitate activities of the order of 10^{-3} to 10^{-4} that found in normal human liver. Preliminary results indicate that use of this extremely sensitive assay may permit demonstration of a constant difference between the group of cystathionine synthase deficient patients who respond clinically and biochemically to large doses of vitamin B_6 and the group of cystathionine synthase deficient patients who do not so respond. The difference is of a type which is compatible with the postulate, presented in the previous annual report, that response to B_6 is due to a stimulation of residual cystathionine synthase activity from 1-2% of normal up to 3-4% of normal. Definitive proof of this postulate is expected to be of general importance in consideration of metabolic diseases since it offers a therapeutic approach to these diseases which has been largely neglected, yet which may be in some cases the optimal means of treatment.

Scientific Significance: Discussed under individual headings above.

Proposed Course of Research: The different lines of work will be pursued as suggested above.

Honors and Awards: Invited to lecture upon "Homocystinuria: the known causes" at Symposium, Society for the Study of Inborn Errors of Metabolism, Belfast, Northern Ireland, July 1-3, 1970.

Publications:

Mudd, S. H., Edwards, W. A., Loeb, P. M., Brown, M. S., and Laster, L., Homocystinuria due to cystathionine synthase deficiency: the effect of pyridoxine, J. Clinical Investigation, 49: 1762, 1970

Mudd, S. H., Pyridoxine-responsive genetic disease, Fed. Proc., 1971 (in press)

Mudd, S. H., Levy, H. L., and Morrow, G.,III, Deranged B_{12} metabolism: effects on sulfur amino acid metabolism. Biochem. Med. 4: 193, 1970.

Mudd, S. H., Uhlendorf, B. W., Hinds, K. R., and Levy, H. L., Deranged B_{12} metabolism: studies of fibroblasts grown in tissue culture. Biochem. Med. 4: 215, 1970.

Goodman, S. I., Moe, P. G., Hammond, K. B., Mudd, S. H., and Uhlendorf B. W.: Homocystinuria with methylmalonic aciduria: two cases in a sibship. Biochem. Med. 4: 500, 1970.

Mudd, S. H., Homocystinuria: the known causes, In Some Inherited Disorders of Sulphur Metabolism, N. A. J. Carson and D. N. Raine, Eds. (E. & S. Livingstone, Edinburgh, 1971) (in press).

Mudd, S. H., Biochemical Mechanisms in methyl group transfer. In Metabolic Conjugation and Metabolic Hydrolysis, W. H. Fishmen, Ed. (Academic Press, Inc., New York, Volume 3, 1971) (in press)

Serial No. M - LGCB 48
1. Laboratory of General and Comparative Biochemistry
2. Section on Alkaloid Biosynthesis
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Transsulfuration in Higher Plants

Previous Serial Number: Same

Principal Investigators: John Giovanelli, Ph.D. and Anne H. Datko, Ph.D.

Other Investigators: S. Harvey Mudd, M.D. and Lowell D. Owens, Ph.D.

Cooperating Units: Agricultural Research Service, USDA

Man Years

Total: 2-1/6
Professional: 2-1/6
Other: 0

Project Description:

Objectives: Previous work has shown that extracts of spinach and other higher plants catalyze the synthesis of homocysteine (and methionine) by two main pathways - a direct sulfhydration pathway and a transsulfuration pathway. The long-range objective of the project is to determine the relative physiological significance and the mechanisms of control of these pathways. The problem is being attacked along three main lines:

(1) A study of the enzymes involved in the two pathways.
(2) In vivo evaluation of the relative physiological significance of the two pathways by use of inhibitors that specifically block one of the pathways.
(3) Physiological and biochemical studies with algae (wild type), and algal mutants in which the biosynthesis of homocysteine and methionine is affected.

Methods Employed: Most of the methods employed have been described in previous reports. O-Phosphoryl-L-homoserine was synthesized enzymically with a partially purified preparation of yeast homoserine kinase, and purified by chromatography on Dowex 1. Preliminary experiments with O-malonylhomoserine-^{14}C indicate that the method of Hendrickson, Giovanelli & Mudd (1970) can be readily modified for the synthesis of radioactive preparations of O-acyl amino acids. Biosynthesis of O-phosphorylhomoserine, O-malonylhomoserine, O-succinylhomoserine and O-acetylhomoserine was assayed by incubation of enzyme with radioactive homoserine and either ATP, malonyl CoA, succinyl CoA, or acetyl CoA,

respectively. After the reaction is complete, the radioactive O-acylhomoserine product is converted to the corresponding N-acylhomoserine derivative and isolated on a column of Dowex 50 H^+. Radioactive O-phosphoryl-homoserine can be isolated without prior conversion to N-phosphorylhomoserine. The in vivo effect of rhizobitoxine on plant seedlings was studied as follows. Spinach seedlings were allowed to absorb rhizobitoxine through the roots, and the level of β-cystathionase was determined at various time periods. Two days after application of rhizobitoxine (when symptoms of toxification begin to appear) a pulse of sulfate ^{35}S was fed through the roots, and the pattern of incorporation of radioactivity into sulfur amino acids determined.

Major Findings: (1) Considerable effort has been devoted to defining optimal conditions for the enzymic synthesis of cystathionine. The specific activity of cystathionine synthase in crude extracts of spinach (as now measured) is over 100 fold greater than that originally reported, and is comparable to that in extracts of Neurospora. Such high rates add significance to the transsulfuration pathway. Extracts from a variety of plants are most active with O-malonylhomoserine, but appreciable activity is always observed with O-succinylhomoserine and O-oxalylhomoserine. O-Acetylhomoserine is relatively inactive, and no significant activity is observed with homoserine.

Parallel studies were initiated to determine which O-acylhomoserine derivatives are synthesized by extracts of higher plants. All efforts to demonstrate the synthesis of O-malonyl-, O-succinyl- and O-acetyl-homoserine in extracts of a variety of plants were unsuccessful. O-Acetylhomoserine synthesis could, however, be demonstrated in extracts of young pea pods, where it is known to accumulate. The significance of the synthesis of O-acetylhomoserine in young pea pods is at present unknown, since it is a relatively inactive substrate for cystathionine synthesis.

The above results suggest that O-malonyl-, O-succinyl- and O-acetylhomoserine are probably not of physiological significance in cystathionine synthesis in higher plants. It is still possible that O-oxalylhomoserine is synthesized in plant extracts, and therefore of physiological significance in cystathionine synthesis. However, it has not yet been practical to assay the synthesis of O-oxalylhomoserine, since a preparation of oxalyl CoA is not at present available.

An insight into the physiological substrate for cystathionine synthesis in higher plants has recently been provided by the observation that plant extracts rapidly synthesize O-phosphorylhomoserine, which in turn is utilized for cystathionine synthesis at a rate approaching that with O-malonylhomoserine. Such a role for O-phosphorylhomoserine in higher plants is of great comparative biochemical interest, since other taxa use either O-succinylhomoserine (bacteria) or O-acetylhomoserine (fungi).

(2) Inactivation of β-cystathionase by rhizobitoxine proceeds by an active-site-directed irreversible inhibition (see previous annual reports). Limited *in vitro* studies indicated that rhizobitoxine is specific for β-cystathionase, as would be expected for this type of inhibition. Contrary to expectations, preliminary results with toxified spinach plants have shown that the level of β-cystathionase in the leaves remains essentially unchanged, and that no significant accumulation of cystathionine ^{35}S occurs. These results suggest that β-cystathionase is relatively insensitive to rhizobitoxine *in vivo*, and represent an interesting example of a markedly different effect of an inhibitor *in vitro* and *in vivo*. Corn seedlings provide an experimental system in which similar studies may be repeated and refined to include individual tissues. Such studies are now in progress.

(3) The design, fabrication and testing of sophisticated equipment for algae culture has been completed, and batches of *Chlorella* (wild type) are at present being collected for extraction of enzymes. A number of ethionine-resistant mutants of *Chlorella* have been isolated by Dr. Owens.

Scientific Significance: Discussed under individual headings above.

Proposed Course of Research: (1) Oxalyl CoA will be synthesized chemically and used for determination of O-oxalylhomoserine synthesis in extracts of higher plants. Parallel studies on the biosynthesis of O-esters of homoserine and their activity in cystathionine synthesis will be extended to a range of evolutionary lines in the plant kingdom, so that the significance of O-phosphorylhomoserine (and other O-esters of homoserine) in the synthesis of sulfur amino acids can be evaluated.

(2) Corn seedlings will be used to confirm the apparent insensitivity of β-cystathionase to rhizobitoxine *in vivo*. Definitive proof of this phenomenon will necessarily result in a reassessment of the value of this inhibitor for *in vivo* studies of transsulfuration.

(3) If algae prove to utilize phosphorylhomoserine in the same manner as higher plants, a variety of physiological and genetic studies will be undertaken in these organisms.

Honors and Awards: None

Publications:

Hendrickson, H. R., Giovanelli, J., and Mudd, S. H.: The synthesis of O-acylamino acids. *J. Org. Chem.* 35: 4270-4273, 1970.

Giovanelli, J. and Mudd, S. H.: Transsulfuration in higher plants. Partial purification and properties of β-cystathionase of spinach. *Biochim. Biophys. Acta* 227: 654-670, 1971.

Giovanelli, J., Owens, L. D., and Mudd, S. H.: Mechanism of inhibition of spinach β-cystathionase by rhizobitoxine. Biochim. Biophys. Acta 227: 671-684, 1971.

Serial No. M-NB-1
1. Lab of Neurobiology
2.
3. Bethesda, Maryland and Woods Hole, Mass.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Transient changes in extrinsic fluorescence of nerve produced by electric stimulation

Previous Serial Number: Same

Principal Investigators: Ichiji Tasaki, M.D., Akira Watanabe, M.D. Mark Hallett, M.D. and Ronald Sandlin

Cooperating Units: Marine Biological Laboratory, Woods Hole, Mass.

Man Years

Total:	4.8
Professional:	3.5
Other:	1.3

Project Description

Objective: One of the main objectives of this laboratory has been the analysis of the macromolecular structure of the nerve cell membrane and the changes in that structure during excitation. Recently we have utilized the technique of extrinsic fluorescence with hopes of extending this analysis. After several years of work, and the development of our own instrumentation, transient changes in extrinsic fluorescence (called optical signals) were demonstrated with a variety of dyes. The objective of this past year was to study the details of these optical signals to see what they could reveal about membrane structure.

Methods Employed: Giant axons from the squid were used in most experiments; nerve trunks from crab and lobster were also employed. The dyes which received most attention belong to a class known as the hydrophobic probes and include 2-p-toluidinylnaphthalene-6-sulfonate (TNS) and 1-anilinonaphthalene-8-sulfonate (ANS). External staining was carried out by soaking the nerve in a solution of the dye. Internal staining of the squid axons was usually accomplished by injecting a small volume of dye into the axon interior.

The stained nerve was mounted in a black Lucite chamber which was specially designed for simultaneous electrical and optical measurements. Electrical stimulation and recording could be

extracellular via two pairs of platinum wires or internal via an electrode made of two platinum wires twisted together which was inserted longitudinally into the axon. The nerve chamber was placed inside a refrigerator to maintain a steady low temperature.

The excitation light originated in a 200 W xenon-mercury source and was focused onto the nerve by means of lenses and diaphragms through one wall of the refrigerator. Interference filters were used to select a quasi-monochromatic beam to excite the dye molecules at an absorption maximum. Fluorescent light was detected with a photomultiplier at 90° to the excitation beam. A secondary filter was placed between the nerve and the phototube to select part or all of the fluorescent light for study and to block all of the scattered excitation light. In experiments of fluorescence polarization, a polarizer was inserted into the excitation light path and an analyzer was inserted into the emission light path.

In order to reduce the effect of fluctuations in the intensity of the light source, a small part of the exciting light was reflected to a second photomultiplier. The output of the main photomultiplier was modified by the output of the second photomultiplier through a differential amplifier. The output of this amplifier was fed to a CAT computer for signal averaging. Optical signals could be detected on the computer after averaging approximately 5000 trials.

Major Findings: The transient decrease in the fluorescence of axons internally stained with TNS associated with the action potential was examined in detail. With the polarizing axis of the polarizer placed parallel to the longitudinal axis of the nerve, the degree of polarization was measured. [The degree of polarization, P, is defined as $(I' - I'')/(I' + I'')$, where I' and I" are the fluorescent intensities with the analyzer parallel and perpendicular to the polarizer respectively.] P was found to be 0.2 for the fluorescence of the nerve in the resting state while P was close to 1.0 for the optical signal.

The spectrum of fluorescence from the axon at rest was found to be broad with a maximum of 450-460 nm. The spectrum of the optical signal involved only the short wavelength part of the resting state spectrum and peaked at 430-440 nm.

Optical signals were produced in TNS-stained axons with voltage clamp pulses. In response to hyperpolarizing pulses there was an increase in fluorescence intensity. With depolarizing pulses there was a decrease in fluorescence. The fluorescence-voltage relation was determined. Tetrodotoxin (TTX) was found to decrease the magnitude of the initial portion of

the optical signal produced by a depolarizing clamping pulse.

The hyperpolarizing response in the KCl-depolarized axon was shown to be associated with a transient increase in TNS fluorescence.

Studies of the degree of polarization were made also with ANS and pyronin B. The ANS optical signal does not exhibit a high value of P while the initial part of the biphasic pyronin B signal has a P similar to that of TNS.

Voltage clamp studies were made with other dyes. The fluorescence-voltage relation of ANS was shown to be similar to that of TNS.

Preliminary studies were made with nerves stained with 4-methylumbelliferone and pyrene-3-sulfonic acid.

Significance: The interpretation of the optical signals can, to a large extent, be made in terms of membrane structure. In general this is true because the physico-chemical factors which influence the fluorescence of the dyes used are well-established. (Much of this physical chemistry has been reproduced in this laboratory over the past year.)

When a hydrophobic probe, like TNS, is dissolved in water its fluorescence is weak and the spectral distribution of its fluorescence is broad. If, on the other hand, TNS is dissolved in a hydrophobic medium, its fluorescence is enhanced and the spectral distribution narrows and peaks at a shorter wavelength. Using this as explanation, the results of our experiments on TNS imply directly that the axonal membrane in the resting state has a hydrophobic nature. In the active state these TNS molecules are no longer in a hydrophobic microenvironment. Thus either the TNS molecules are expelled from the membrane (implying loss of hydrophobic binding forces) or the membrane undergoes a conformational change from hydrophobic to hydrophilic.

Since the fluorescence-voltage curve is similar in detail to the conductance-voltage curve, the deduction can be made that the optical signal is related to conductance. From the earlier conclusions on the meaning of the spectral data, the interpretation can be made that a change in conductance is due to a hydrophobic-hydrophilic transformation in the membrane.

The fluorescence polarization information was unexpected and striking. There seems no alternate interpretation other than the membrane has a highly structured and ordered macromolecular nature. The membrane must be able to allign the dye molecules

quite exactly so that their long axes are parallel to the longitudinal axis of the axon.

Proposed Course: Further detailed analysis will be made of the fluorescence intensity and spectrum from the TNS-stained axons in order to get an estimate of the number of binding sites in the membrane for TNS. Other dyes whose fluorescence is influenced by features other than polarity will be studied to learn about other features of the membrane macromolecular structure. An attempt will be made to demonstrate optical signals associated with other physiological phenomena, like the bi-ionic action potential.

Honors and Awards:

During the past year Dr. Tasaki was an invited speaker at:

University of Alabama
Cornell University College of Medicine
American Academy of Neurology meeting, Bal Harbour, Florida
University of California Medical College, Los Angeles
University of Arizona Medical College
First discussion conference on, "Models of Biopolymer Structure and Functions," sponsored by the Institute of Macromolecular Chemistry, Czechoslovakia Academy of Sciences

In addition Dr. Tasaki was a Visiting Professor at the Instituto di Fisica, Genova, Italy.

Dr. Watanabe participated in the Franklin C McLean conference on, "Cellular mechanism for calcium transfer and homeostasis.

Publications:

Conti, F. and Tasaki, I.: Changes in extrinsic fluorescence in squid axons during voltage-clamp. Science, 169: 1322-1324, 1970.

Tasaki, I.: Effects of ultraviolet and visible light on nerve fibers and changes in optical properties during nervous activity. In Lawrence, J.H. and Hamilton, J.G. (Eds.): Advances in Biological and Medical Physics, Vol. 13, New York and London, Academic Press, 1971, pp. 307-327.

Serial No. M-NB-2
1. Lab of Neurobiology
2.
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Sensory-motor integration in the primate visual system

Previous Serial Number: Same

Principal Investigators: Robert H. Wurtz, Ph.D. and
Michael E. Goldberg, M.D.

Man Years

Total:	3.8
Professional:	2.0
Other:	1.8

Project Description

Objective: In the past year we have continued our study of the problem of how the brain processes visual and visual motor information. We have first studied the detailed organization of the visual receptive fields of cells in the upper layers of the superior colliculus of the monkey. We then studied how the visual response was modified when the monkey attended and responded to the stimulus, rather than ignoring it.

Methods Employed: Rhesus monkeys were trained to look at a spot of light projected on a screen in front of them; the monkeys were rewarded if they released a bar when the light dimmed. The light was small enough and the dim subtle enough that their eyes were fixated upon the spot, and their normal large spontaneous eye movements were suppressed during the fixation periods. The monkeys did not move their eyes even when a second spot of light, large or small, was flashed on the screen. If their first fixation spot disappeared, however, they then made a rapid eye movement (saccade) to fixate their eyes upon a second spot of light on the screen. The eye movements were monitored using a D.C. electrooculogram. After training was completed, the activity of single cells was studied using the recording methods developed by E.V. Evarts, which allow the study of response properties of brain cells during behavior in an awake animal rigidly restrained only by its head, with its limbs free to move. At the end of the experiment histological sections are made of the brain in order to determine the location of cells studied.

Major Findings: All cells considered in this report were in the optic layer and superficial grey layer of the superior colliculus. All responded to light. The response properties of the cells were worked out while the monkey fixated his eye upon a spot of light by seeing over what area a second spot of light would influence the discharge characteristics of the cell. The neurons were divided into two classes on the basis of several differences in their response to light during fixation.

The first type of cell responded to a stationary spot of light in an area of a visual field and to movement of the same spot in any direction within that area. The size of this receptive field area varies from a few degrees on a side to as much as 30-40 degrees on a side. While the area is large, a small stationary spot of light (1 degree of arc in diameter) placed anywhere in the receptive field of the cell produces an increased rate of cell discharge. The shape or orientation of the light stimulus has little effect on the cell response. For some of these cells, a large spot of light projected over the entire receptive field and the surrounding area produces either no response at all or a clear decrement in the cell's rate of impulse discharge; these cells therefore have a clear inhibitory surround area. Other cells of this type continue to show a response to stimuli covering an area much larger than the receptive field area determined by a small spot of light; these cells apparently have no inhibitory surround area. About 90% of the cells studied were of the first type.

The second type of cell responded better to stimuli moving through their receptive fields in certain directions than in other directions. For example, the cell would show an increased discharge to a light stimulus moving from left to right but would be inhibited by a stimulus moving from right to left. These cells generally did not respond as well to a stationary stimulus as to a moving stimulus. Of the cells studied, 10% were this second type.

Once the receptive field of a cell was determined, a subsequent experiment was then performed on the first type of cell, those that respond well to a stationary stimulus. The response of a cell to a spot of light coming on at a particular point in the receptive field was determined over at least 20 trials. Then the spot of light in the receptive field (receptive field spot) was made more significant for the monkey by the following procedure: the fixation point was turned off at the time when the receptive field spot was turned on. In response to this procedure the monkey made a rapid eye movement to the receptive field spot as he had been trained to do, instead of ignoring it as before. The monkey now had to pay attention to the spot of light in order

to make an eye movement to it.

In the 200-300 msec of reaction time between the appearance of the spot of light in the receptive field and the eye movement to it, the receptive field spot fell on the previously studied place in the receptive field. In this case, however, the units responded to the stimulus onset with a more vigorous discharge. When the monkey was paying attention to the stimulus the initial response to the stimulus coming on had shorter interspike intervals or more discharges, or there was a more prolonged response to the stimulus, or the overall response was no better but just more regular. The type of response which occurred with attention varied between monkeys: one monkey showed primarily a more regular response to the stimulus when he had to pay attention to it; the other monkey showed primarily an enhanced late response when he had to pay attention to the stimulus. The enhancement of the cell response associated with an eye movement to the stimulus occurs for points throughout the receptive field. If the monkey moves his eyes to another stimulus outside the receptive field there is also a slight enhancement but never as great as with an eye movement to a point within the field.

Significance: The majority of cells in the optic and superficial grey layers of the superior colliculus have receptive fields which do not require a very specific visual stimulus: any position within a large area, any direction of movement, or any shape or orientation, will be effective as stimulus. This is in striking contrast to the cells in visual cortex cells we have studied previously that require all these variables to have certain values before the response occurs. The superior colliculus cells would seem to have great value in determining that something is in a part of the visual field but not at all what it is.

Many of these same cells show an enhanced response when the monkey had to attend to the receptive field stimulus in order to make an eye movement to it. Prior to these experiments, it was possible to study only the stimulus effect on the cell either because the animal was paralyzed or because the animal was not trained to attend to the stimulus. With these experiments we see that attention does alter the cell's response even though the physical properties of the stimulus stays exactly the same. The attention effect does not significantly alter the receptive field of the cell but instead enhances the response of the cell to stimuli within the field. The net effect of this selective enhancement by attention is probably a more reliable transmission of information to higher levels of the nervous system.

Proposed Course: We intend to determine whether the attention effect we have studied in the superior colliculus is also present in the visual area of cerebral cortex. In addition we plan to

see if other extra-visual inputs such as those related to eye movements might also impinge on these superior colliculus cells with clearly established receptive fields.

Honors and Awards:

During the year Dr. Wurtz was an invited speaker at:

Mental Health Research Institute, University of Michigan
Massachusetts Institute of Technology

Dr. Goldberg was invited to speak at the Harvard Medical School

Publications:

Wurtz, R.H. and Goldberg, M.E.: Superior colliculus cell responses related to eye movements in awake monkeys. Science, 171: 82-84, 1971.

Serial No. M-NB-3
1. Lab of Neurobiology
2.
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Metabolic activity of nuclear proteins from rat brain cells

Previous Serial Number: Same

Principal Investigator: José A Burdman, M.D.

Man Years

Total:	2.0
Professional:	1.8
Other:	0.2

Project Description

Objective: The objectives of the present study were: (a) to investigate intranuclear sites of protein synthesis in brain cells, (b) to explore the possible relationship between rate of synthesis of nuclear proteins and physiological stimulation of the brain, and (c) to investigate the relationship between the rate of cell division in the brain with the metabolic activities of nuclear proteins.

Methods Employed: (a) In vitro: Nuclei were purified from brain cells of adult and young rats and incubated in media containing [^{3}H] leucine. After 15 minutes of incubation, enough non-radioactive leucine was added to the incubation mixture to make further incorporation of the isotope negligible. Nuclei were sedimented by centrifugation and nuclear proteins differentially extracted according to their solubility at different ionic strength and pH. The specific radioactivity of the proteins in the nuclear fractions was measured.

(b) In vivo: Adult and young rats were injected intraperitoneally with [^{3}H] leucine or [^{3}H] thymidine and sacrificed at various times after injection. Subcellular components from the brain were fractionated by differential and sucrose gradient centrifugation. Nuclear proteins were extracted from the purified nuclei according to the solubility at different ionic strength and pH. The specific radioactivity of the proteins and the DNA in subcellular and nuclear fractions was measured.

Major Findings: (a) The in vitro experiments indicated that there are several sites of protein synthesis in nuclei from brain cells. After chasing with non-radioactive leucine there was no migration of radioactive proteins among the different nuclear fractions.

(b) Stimulation with flashing light did not result in any significant change in the rate of synthesis of nuclear proteins in the visual cortex.

(c) During post-natal development of the brain, the rate of cell division reached its peak at about the 8th day. The rate of synthesis of nuclear proteins was higher in the 8 day old than in the newborn rat. This increased rate of protein synthesis during the first 8 days after birth was considerably higher in the nuclear fraction than in any other subcellular fraction from the brain (mitochondrial, microsomal and soluble). This increase in protein synthesis was especially marked in those nuclear proteins which are associated with the DNA. Electrophoretically, no major differences could be observed between nuclear proteins from the newborn brain and the 8 day old brain.

Proposed Course: Further studies will be performed (a) to investigate the role of nuclear proteins on DNA synthesis in the brain, and (b) to investigate qualitative differences between nuclear proteins from neurons and those from glial cells.

Significance: Cell multiplication in the central nervous system of mammals takes place mainly during intrauterine life and the first two weeks after birth, although a limited degree of proliferation of glial cells continues into adult life. The reason for the inability of differentiated neurons to undergo cell division is not known. Nuclear proteins are closely associated with the DNA and they might be important in the regulation of DNA synthesis. The rate of synthesis of DNA associated proteins in the brain parallels the rate of DNA synthesis and in this way these proteins might be necessary for cell division to occur in nerve cells. The diminished synthesis of DNA associated proteins in mature neurons could result in the absence of certain proteins which are involved in DNA replication. This, in turn, might be important in explaining the intracellular sequence of events leading to mitosis or suppression of mitosis in nerve cells.

Publications:

Burdman, J.A.: Incorporation in vivo of radioactive leucine into neuronal and glial nuclear proteins of rat brain. J. Neurochem., 17: 1555-1562, 1970.

Burdman, J.A., Haglid, K. and Dravid, A.R.: Protein synthesis in fractions from isolated brain cell nuclei. J. Neurochem., 17: 669-676, 1970.

Serial No. M-NC-1
1. Neurochemistry
2.
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Conversion of Phenylalanine to Tyrosine

Previous Serial Number: M-NC-1

Principal Investigator: Seymour Kaufman

Other Investigators: Daniel Fisher, Paul Friedman, E. Stanley Hall, Charles Huang

Man Years

Total	: 4
Professional	: 3
Other	: 1

Project Description:

Objectives: The oxidation of foodstuffs, which ultimately supplies the energy for all cellular functions, can be effected by two completely different processes. Organic compounds can either be oxidized by dehydrogenation, the removal of hydrogen, or by oxygenation, the addition of oxygen to the substrate molecule. The first type of reaction predominates in carbohydrate and fat metabolism. The mechanism of this kind of oxidation has been the subject of investigation for 50 years and is now quite well understood. Oxygenation reactions are encountered mainly in the cellular catabolism of ring compounds such as aromatic and heterocyclic amino acids, hormones and drugs. In contrast to hydrogenations, the mechanism of oxygenation reactions has remained obscure. The conversion of phenylalanine to tyrosine is an oxidation reaction of this type and the goal of this study is to gain insight into the mechanism of this kind of oxidation reaction.

Methods Employed: Standard methods of protein purification, including salt and ethanol fractionation, ion-exchange chromatography and sephadex-gel filtration, have been used. The following methods of protein analysis have been used to characterize the hydroxylase: sucrose-density ultracentrifugation and polyacrylamide gel electrophoresis.

Major Findings: The availability of essentially pure phenylalanine hydroxylase from rat liver has permitted experiments to be carried out with stoichiometric amounts of the enzyme. These experiments have provided new insight into the mechanism of reaction catalyzed by the enzyme. It has been shown that the reaction is not of the "ping-pong" type, i.e., there is no evidence for a reduced enzyme intermediate.

The mechanism of this hydroxylase is, therefore, clearly different from that of dopamine β-hydroxylase, where we had previously shown that a reduced enzyme is an intermediate.

Preliminary evidence indicates that phenylalanine hydroxylase is an iron-enzyme. The catalytically-inactive iron-free apoenzyme has been prepared. About a dozen different metals have been tested for their ability to reactivate the enzyme; iron is the only one that is effective.

It was previously found that one of the substrates, phenylalanine, inhibits the hydroxylase only in the presence of the naturally-occurring cofactor, biopterin. It has now been found that the same is true for the other substrate, oxygen. Inhibition is manifest at atmospheric oxygen tensions.

Phenylalanine hydroxylase has been detected in the liver of a 23 week-old human fetus. The kinetic properties of the fetal enzyme are indistinguishable from that of the hepatic enzyme from adults. The enzyme has also been detected in fetal guinea pig liver during the second half of the gestation period. This pattern of development of the hydroxylase is markedly different from that of the rat where hydroxylase is not detectable until the day before birth.

Scientific Significance: The demonstration that the mechanism of phenylalanine hydroxylase is not of the "ping-pong" type rules out a common type of reaction pathway for this enzyme and proves that even within the group of hydroxylases, there are different fundamental mechanisms operating. The finding that the hydroxylase is an iron-enzyme is the first implication of this element in a whole series of metabolic pathways, including those leading to the biosynthesis of the catecholamine neurohormones.

The finding that the hydroxylase is sensitive to inhibition by oxygen raises the possibility that other pterin-requiring hydroxylases such as tyrosine and tryptophane hydroxylases may also share this property. If this proves to be the case, the inhibition of this group of enzymes by oxygen may explain, in part, the known toxicity of oxygen to the nervous system.

During the course of a study of the development of hepatic phenylalanine hydroxylase, two strikingly different patterns have been detected: in the rat, the enzyme does not appear until the day prior to birth, whereas in the human and the guinea pig, activity is detectable during the second half of the gestation period. Based on our results, it is clear that for a study of the factors that may regulate the development of hepatic phenylalanine hydroxylase in the human, the guinea pig is a more appropriate model than the rat. The results also show that in all species tested, the hydroxylase reaches the adult level before or during the first day of life. One of the benefits derived from this early maturation of the enzyme is that it provides immediate protection to the organism against the toxic effects of high levels of phenylalanine.

Proposed Course: Further studies on the mechanism and regulatory properties of the enzyme will be carried out. The function of the iron in the enzyme will be investigated.

Honors and Awards: None

Publications:

Kaufman, S. and Fisher, D. B.: Purification and some physical properties of phenylalanine hydroxylase from rat liver. J. Biol. Chem. 245: 4745-4750, 1970.

Kaufman, S.: A protein that stimulates rat liver phenylalanine hydroxylase. J. Biol. Chem. 245: 4751-4759, 1970.

Kaufman, S., Storm, C. B., and Fisher, D. B.: Studies on the mechanism of the enzymatic conversion of phenylalanine to tyrosine. In Iwai, K., Akino, M., Goto, M., and Iwanami, Y. (Eds.): Chemistry and Biology of Pteridines, Proceedings of the IVth International Symposium on Pteridines, July 1969. Tokyo, International Academic Printing Co., Ltd., 1970, pp. 209-216.

Kaufman, S.: Phenylalanine hydroxylase. In Tabor, H. and Tabor, C.W. (Eds.): Methods in Enzymology, N.Y., Academic Press, 1970, Vol. XVII, pp. 603-609.

Publications, continued

Kaufman, S.: Enzymatic assay for 7,8-dihydrobiopterin. In McCormick, D. B. and Wright, L. D. (Eds.): Methods in Enzymology, N.Y., Academic Press, 1971, Vol. XVIII, pp. 614-618.

Serial No. M-NC-2
1. Neurochemistry
2.
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biosynthesis of Catecholamines

Previous Serial Number: M-NC-2

Principal Investigator: Thomas A. Lloyd

Other Investigator: Seymour Kaufman

Man Years

Total	1.25
Professional	1.25
Other	0

Project Description:

Objectives: These investigations are a continuation of previous work in this laboratory concerning the biosynthesis of catecholamines. Since tyrosine hydroxylase has been demonstrated to be the rate limiting step in the biosynthesis of catecholamines, present goals include: a further delineation of the subcellular distribution of this enzyme, a purification of tyrosine hydroxylase to homogeneity, and a comparison of the physical and biochemical properties of this enzyme to those of highly purified phenylalanine hydroxylase.

Methods Employed: Partially purified tyrosine hydroxylase from bovine adrenal medulla has been used to study the role of tetrahydrofolate as a cofactor for pterin-dependent hydroxylases. Qualitative organic chemistry functional tests, analytical thin-layer chromatography, gas-liquid chromatography followed by mass spectrometry, and specific enzymological tests have been used to determine the purity of freshly reduced tetrahydrofolate and the nature of a contaminant associated with tetrahydrofolate.

Major Findings: In earlier studies on the phenylalanine and tyrosine hydroxylation systems, tetrahydrofolate was generally prepared by the catalytic reduction of folate. We have found that the tetrahydrofolate so generated is contaminated with a reduced, unconjugated pterin which apparently is formed as a degradation product of tetrahydrofolate during the course of the reduction. This contaminant was separated from authentic tetrahydrofolate by DEAE-cellulose column chromatography. The cofactor activity of the original mixture and the two purified fractions were compared in both the tyrosine and phenylalanine hydroxylase systems and the contaminant found to be responsible for 65-90% of the cofactor activity of the unresolved mixture. Further studies revealed that the contaminant represented only 1% of the original mixture.

Enzymatic, chemical and physical methods were employed to unambiguously characterize both the contaminant and authentic tetrahydrofolate. The contaminant was identified as 2-amino-4-hydroxy-6-methyltetrahydropterin.

Scientific Significance: Ever since the hydroxylation cofactor activity of tetrahydrofolate with phenylalanine hydroxylase was discovered, the question of whether this compound played the same role in vivo has remained unanswered. The subsequent finding that the naturally-occurring cofactor in liver is an unconjugated pterin, reduced biopterin, suggested that the answer to this question might be negative, but still left it open. The present demonstration that most of the hydroxylation cofactor activity of tetrahydrofolate, with both phenylalanine and tyrosine hydroxylases, is due to its contamination with 6-methyltetrahydropterin, provides a convincing answer to that question: the hydroxylase cofactor activity of tetrahydrofolate is probably too small to be of any physiological significance.

Proposed Course: Further studies are in progress on the purification of tyrosine hydroxylases from different organs and species along with a comparison of the cofactor specificities of these isolated enzymes. Preliminary investigations suggest that the biosynthesis of catecholamines is affected, and possibly regulated, by the nature and proximity of the reduced pteridine cofactor.

Honors and Awards: None

Publications:

Shiman, R., Akino, M., and Kaufman, S.: Solubilization and partial purification of tyrosine hydroxylase from bovine adrenal medulla. J. Biol. Chem. 246: 1330-1340, 1971.

Lloyd, T., Mori, T., and Kaufman, S.: 6-Methyltetrahydropterin: Isolation and identification as the highly active hydroxylase cofactor from tetrahydrofolate. Biochemistry, in press. (June 1971)

Shiman, R. and Kaufman, S.: Tyrosine hydroxylase. In Tabor, H. and Tabor, C. W. (Eds): Methods in Enzymology. N.Y., Academic Press, 1970, Vol. XVII, pp. 609-615.

Serial No. M-NC-4
1. Neurochemistry
2.
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Biochemical Basis of Skeletal Muscle Hypertrophy

Previous Serial Number: M-NC-4

Principal Investigator: Seymour Kaufman

Other Investigator: Charles Jablecki

Man Years

Total	: 2.50
Professional	: 1.50
Other	: 1

Project Description:

Objectives: The objective of this project is unchanged: The elucidation of the biochemical correlates of cellular hypertrophy.

Methods Employed: We are using an operation to produce work-induced hypertrophy of skeletal muscle in vivo as previously described. The biochemical fractions of interest are labeled isotopically. RNA is separated by a modified Schmidt-Tannhauser procedure and phospholipids and their precursors by the Folch procedure.

Major Findings: RNA studies. Previous work in this laboratory on the uptake in vivo of an RNA precursor (orotic acid) has shown a significant increase 24 hours after the initiation of work-induced hypertrophy of skeletal muscle. This work is being extended to earlier points in the time course of hypertrophy and also to localize this change to the cell types present in muscle. We have achieved specific labeling of mammalian RNA by injecting cold thymidine simultaneously with tritium labeled uridine. This method gives over 15,000 dpm/100 mg wet weight muscle, an activity sufficient for autoradiography.

Phospholipid Studies. Within one hour following tenotomy, the uptake of P^{33} is greatly enhanced (two-fold) in hypertrophying muscle. This early change is not specific to hypertrophy, however, and has been reported in muscle following the administration of insulin as well as following mild exercise that does not lead to hypertrophy. The change in phosphorus uptake has complicated the interpretation of phospholipid labeling in muscle during hypertrophy, but a significant alteration in the pattern of labeling has been recorded as early as two hours after tenotomy.

Scientific Significance: Specific labeling to a high activity of RNA in mammalian tissue provides a method for localizing by autoradiography changes in RNA metabolism. A general method for doing this in mammals has emerged from our study.

The changes in the pattern of labeling of phospholipids are the earliest that have yet been detected in muscles undergoing hypertrophy; they are detectable 1-1/2 - 2 days before hypertrophy is manifest. These results suggest that we are looking at a biochemical event that is close to the physical change that initiates the process of hypertrophy.

Proposed Course: An in vitro model, probably a rat hemidiaphragm preparation, will be used to follow a biochemical change specific to hypertrophy following its verification in the in vivo model. That change may occur in RNA or phospholipid metabolism, both of which are currently being investigated.

Honors and Awards: None

Publications: None

Serial No. M-NC-5
1. Neurochemistry
2.
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Process of Lysogeny

Previous Serial Number: M-NC-5

Principal Investigator: Howard A. Nash

Other Investigators: Cecilia M. Hidalgo

Man Years

Total	3
Professional	2
Other	1

Project Description:

Objectives: The overall goal of this project is to determine the biochemical steps involved in the integration of viral genes into a host chromosome. This goal has been approached by studying a) the viral protein known to be involved in the integrative act and b) the chemistry of the regions of viral and host chromosomes which are affected by the integration act.

Methods Employed: Microbiological techniques for isolation, growth, genetic characterization of bacteriophages; radioactive and/or density labeling procedures for bacteriophage; buoyant density and sedimentation analysis using density gradients in a high speed preparative ultracentrifuge; thin-layer chromatographic analysis of nucleotide bases; polyacrylamide gel electrophoresis; chromatographic column separations.

Major Findings and Significance:
Part I. The integration of bacterial virus DNA into the genome of its host requires the presence of a phage-coded system given the collective name Int. Previous work in this laboratory and elsewhere has indicated that the Int is involved in promoting recombination between highly specific loci which can be identified both on the genetic and physical map of the lambda chromosome. Genetic and biophysical

studies have been able to delineate certain features of the Int-promoted process but have not been able to provide strong inferences as to its detailed mechanism. We have utilized the double label technique in conjunction with known mutants of the Int gene to begin the isolation and purification of the Int system. We have shown that, in a host irradiated with ultraviolet light to suppress host protein synthesis, the Int gene is expressed as an apparently single polypeptide chain of molecular weight 45,000. The material is both membrane-bound and associated with DNA. After partial purification, Int may be isolated as a large aggregate involving a host protein of small subunit molecular weight.

Part II. The study of Int action of highly specific DNA loci leading to integration is one aspect of the general problem of specific DNA-protein interactions in biological systems. In formulating models for the basis of protein recognition of specific DNA regions, the role of modified nucleotides has been frequently suggested. In the case of host restriction of phage DNA, methylated nucleotides have been shown to play an important role in enzyme recognition of DNA sequence to be degraded or spared. Most organisms contain many more methyl groups than can be accounted for by the needs of host modification and restriction systems. The function of these additional methylated bases may be deduced from a knowledge of their location with respect to known genetic elements. We have performed such a study by examining the distribution of the methylated bases along the genome of bacteriophage lambda. The total number and identity of methylated bases of lambda DNA under conditions of normal growth have been determined. The distribution of these bases between each stand of the double helix has been examined and found to be approximately uniform. On the other hand, the distribution of methylated bases along the length of the lambda genome has shown gross deviations from uniformity. In particular, the two halves of lambda DNA show different contents of methylated bases and this difference is not simply a reflection of the differing guanine-cytosine content. Further, a short region of DNA near the middle of the lambda DNA molecule has been found to be greatly undermethylated.

Scientific Significance:
Part I. The findings described above are in part, a biochemical identification of material which previously had only a genetic identity. Therefore they represent an initial insight into the biochemical mechanism of a process,

which is at once a paradigm for the universal phenomenon of genetic recombination as well as the reversible coexistence of host and viral genomes.

Part II. This study has uncovered a new kind of map of a DNA molecule. In addition to the extant genetic and nucleotide sequence or composition maps, we find there is a methylation map. This fact, together with the established ubiquity of methylated bases in DNA lends strong support to the hypothesis that methylation of DNA is used to designate specific areas of the genome for biochemical action.

Proposed Course: Large scale purification of Int protein will be attempted, following the scheme used for purification of double-labeled material. The purified material will be characterized with special emphasis on interactions with the lambda DNA substrate. The constancy of methylation maps of lambda DNA under a variety of restrictive conditions and physiological states will be examined. Further dissection of the genetic location of the major methylation map features will be attempted.

Honors and Awards: None.

Publications:

Nash, H. A. and Robertson, C. A.: On the mechanism of Int-promoted recombination. Virology, in press.

Serial No. M-NC-6
1. Neurochemistry
2.
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Physicochemical Investigations of Biofunctional Structures of Glycosaminoglycans and Glycolipids A. In the Intercellular Matrix and Interstitial Fluids, B. In the Intracellular Granules Containing Biogenic Amines, and C. In Genetic Diseases Associated with Mental Retardation

Previous Serial Number: M-NC-6

Principal Investigator: Audrey Larack Stone

Other Investigators: A. D. Van Praag, S. Farber, D. F. Bradley
C. A. Dekaban, G. Constantipoulos,
E. Kolodny

Cooperating Units: Dept. of Medicine, N.Y.U. Medical College (A), SN and NC (C)

Man Years

Total	:	0.50
Professional	:	0.50
Other	:	0

Project Description:

I. Physicochemical measurement of optical conformations of glycosaminoglycans (GAG, mucopolysaccharides); and determination of the molecular basis for the formation and maintenance of inter- and intra-molecular structures known to be involved in the rapid transformation of simple cations and biogenic amines from the bound to the active form (e.g., ion and water transport, release of histamine and serotonin from the mast cell, of AcCh from the synaptosome, of the epinephrines from the chromaffin granules); optical studies of GAG and glycolipids from Hurler and Tay-Sach patients and corresponding normal tissues.

Project Subtitle (A, B): Absorption and circular dichroism (CD) of GAG and mixed ganglioside from normal tissues and of their metachromatic complexes with dyes.

Objectives: To elucidate the particulars of the various molecular conformations by means of their recently discovered (M-NC-21, 1967) ultraviolet amide transition bands and the special optical effects of their dye complexes (M-NC-21, 1965) with the view towards developing a sensitive method of identification, and a molecular basis for biological activities associated with interstitial matrices such as the greater neuronal membrane.

Major Findings: Standard GAG exhibit particular CD in the spectral region of the n-π and π-π amide transitions. Two general patterns emerge which can be correlated with a structural difference in the linkages of the amino sugars: (1) occurs with polymers containing 1-3 linked glycosamino sugars and (2) with glycosamino moieties linked 1-4 by either α- or β-glycosidic bonds. A unifying model considers that the difference in preferred order of the amide groups derives from two forms of secondary conformation (1) and having a linear H-bond from the N(acceptor) and to the (C_2O) O-H of the preceding uronic acid and (2) having a linear H-bond from the N(acceptor) to the (C_2O)O-H or (C_3)O-H of the following sugar. The H-bonds would have similar strength but opposite directions in the two systems, i.e., towards the non-reducing end (1) or towards the reducing end (2).

The CD bands are molecular characteristics which aid in identification. Values for the two groups are: (1) (-) CD at ~208 mμ with unresolved second (-) band, or (2) resolved CD bands, (-) at ~210 mμ and (+) at ~190 mμ, represented by chondroitin sulfate and by heparin, respectively. Conformational changes in hyaluronic acid (HA) (one of the major glycosaminoglycans in the interneuronal membrane matrix) have been demonstrated. This high molecular weight substance forms inter-molecular super structures of varying rigidity. Changes in the optical properties indicate major structural reorganization at lowered pH's. HS has been found in the kidney cortex, isolated at relatively higher salt elution than that exclusively found in other tissues. This type of HS has significance in Hurlers diseases (see below C).

In vitro studies of metachromasy using components of mast cell granule show that histamine does not combine at all negative sites on heparin, while protamine binds tightly to all. Thus, histamine has specific binding regions while the basic polypeptide blocks off total lengths of the heparin molecule. Release of histamine could be explosive upon initiation of binding of protamine-type molecules to heparin.

Scientific Significance: A study of the structure-biology relationship of glycosaminoglycans was started several years ago because it was thought that the mechanisms of intracellular granule expulsion and acetylcholine release at the synapses could be approached using model systems in vitro. The proposed hydrogen bonds in GAG have been considered by other investigators and found to be possible from theoretical energy mapping of various conformations. The dramatic change in HA with pH is consistent with the fact that this GAG was shown (M-NC-6, 1969) from model building to twist in either of the two conformations because of the absence of sulfate groups.

Circular dichroism patterns correlated with salt elution fractions of GAG provide clear aid to identification and characterization of these polymers, especially where substances like heparan sulfate might be overlooked. These methods have already become important to other investigators in the field and collaborative efforts have lead to the finding of large amounts of a rare type of HS in kidney cortex and elucidation of a number of differences among various HS forms in this poorly defined family of GAG substances.

Proposed Course of Project: Specific optical measurements of conformations of GAG with changes in pseudobiological environments will be undertaken with continued structural and conformational studies on the various kinds of HS.

Project Subtitle C1: Physicochemical studies of glycosaminoglycans from patients with generalized mucopolysaccharidosis.

Objectives: To elucidate the biologic level and site of the abnormality by looking at the structure of the accumulating DS (chondroitin sulfate B, or dermatan sulfate) and HS, in comparison with these polymers from normal tissues.

Methods Employed: See Project Subtitles (A,B).

Major Findings: Metachromasy of pathologic mucopolysaccharides with MB differs from that of the normal standards. ORD curves of ChS-B and HS are sufficiently different to provide the basis for analysis of mixtures of these materials from patients. Purified heparan sulfate (HS) from Sanfilippo patients has two main fractions. The optical conformation of one is similar to that of normal HS which supports the view that biosynthetic mechanisms of chain enlargement *per se* are not defective in this genetic disorder, despite a marked decrease in the molecular weight. The optical pro-

perties of the second fraction were unlike normal HS and resembled heparin indicating that there is a separate accumulation of a new type of mucopolysaccharide. Fractions of HS both showed lowered degrees of O-sulfation (which corresponded with the weaker degree of the metachromatic reaction) estimated to occur during the excretion process.

Scientific Significance: The optical methods detect differences in molecular structure so that the several HS fractions from Sanfilippo patients were further distinguished. Although synthetic enzymes appear to be operating normally, defect in branch-linkage or debranching enzymes may be important in the accumulation of the two fractions. This is consistent with subsequent demonstrations of two genetic defects in this disease. The CD of the second fraction points out that a heparin-like heparan sulfate not usually detected in normal tissue, but now found in kidney cortex, may be responsible for certain of the symptoms associated with the Sanfilippo disorder. Since others have suggested a causal relation between HS-accumulation and mental retardation, the finding that the heparin-like fraction appears to be a separate substance is important in consideration of the CNS effects.

Proposed Course: Continued collaboration to elucidate the kinds of GAG within Hurler cells in tissue culture.

Project Subtitle C2. Physicochemical studies of gangliosides from normal mammalian tissues and a patient with generalized gangliosidosis (Tay Sachs).

Objectives: To elucidate conformational relationships among the various gangliosides found in normal brain and peripheral tissues (known to differ slightly in kind and number of neuraminic acid residues) and to compare these with the gangliosides which accumulate in the various genetic disorders.

Methods: See Project Subtitle (A,B).

Major Findings: The CD of the various gangliosides show for major CD bands which contribute in varying proportions to the resultant curve, two from the GalNAC chromophore (- at ~210 mμ and + at ~187 mμ) and two from the NANA or NGNA components (- at ~220 mμ and - at 196 to 202 mμ). Comparisons of the CD parameters revealed characteristic differences between G_{M3} and the more complex gangliosides, and between the two disialo-gangliosides, GD_{1a} and GD_{1b}.

G_{M2} which accumulates in the brain of children with Tay-Sachs disease has optical properties similar to the G_{M2} prepared from rat brain. CMP-NANA, the intermediate in sialyl transferase reactions has an α-ketosidic linkage similar to those in the gangliosides.

Scientific Significance: Characteristic CD's among gangliosides may be used in structural determinations. These studies showed that the Tay Sach's ganglioside(G_{M2}) from normal tissues, which supports the view that the etiology of this gangliosidosis lies exclusively in the absence of the enzyme system and does not include abnormality in the substrate. Furthermore, this method provided the first evidence for the α-ketosidic nature of the CMP-NANA intermediate in the biosynthesis of NANA containing oligomers and polymers, which bears directly upon the enzyme mechanism of stereospecific synthesis, indicating a double inversion as in the case of the biosynthesis of amylose.

Proposed Course: Specific studies are completed. Further studies concerning the ceramide portion of gangliosides are underway.

Honors and Awards:

Elected to Council of the Assembly of Scientists, NIMH Feb. 1971.

Invited 75 minute lecture on the Metachromatic Reaction of Acridine Orange and its Complexes with Biological Polyanions given for the Laboratory of Neurobiology, NIMH, March 1971.

Publications:

Stone, A. L., Constantpoulos, G., Sotsky, S. M., and Dekaban, A.: Optical rotatory dispersion of mucopolysaccharides IV. Optical rotatory dispersion and circular dichroism of glycosaminoglycans and heparan sulfate fractions from the urine of patients with mucopolysaccharidosis (Hurler syndrome). Biochim. Biophys. Acta, 222: 79-89, 1970.

Stone, A. L., Bradley, D. F., and Childers, L. G.: Metachromatic reaction of proflavine bound to DNA and RNA: spectrophotometric titration and quantitative parameters. Trans. Farad. Soc., 66: 3081-3089, 1970.

Stone, A. L., and Kolodny, E. H.: Circular dichroism of mammalian gangliosides from normal and Tay-Sachs tissues. Chem. Phys. Lipids, 7: 46-51, 1971.

Stone, A. L.: Optical rotatory dispersion of mucopolysaccharides and mucopolysaccharide-dye complexes. III. Circular dichroism bands of glycosaminoglycans and gangliosides. Biopolymers, 10: 739-751, 1971.

Van Praag, D., Stone, A. L., and Farber, S. J.: Glycosaminoglycans of rabbit renal cortex. (Abstract) Fed. Proc., May-June 1971.

Serial No. M-NC-7
1. Neurochemistry
2. Physical Chemistry
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The Role of the Cell Membrane in Cellular Organization, A Molecular Study

Previous Serial Number: M-NC-7

Principal Investigator: David M. Neville, Jr.

Other Investigators: Hartmut Glossmann;
Pierre Freychet, NIAMD

Man Years

Total	2.5
Professional	1.5
Other	1

Project Description:

Objectives: The aim of this project is to determine the specific chemical interactions which occur at the surfaces of cells which affect cellular differentiation and cellular organization. Specifically we propose that the recognition which cells have of their environment and neighboring cells is mediated by specific proteins on the surface membranes. Each cell has a specific protein or eigen protein which can be recognized by other cells, signalling the identity of the cell. Our aim is to isolate and purify these proteins and to develop antibodies to them. By adding purified eigen proteins or eigen protein antibodies to cellular systems we aim to alter patterns of cellular organization and behavior.

Methods Employed: Ultracentrifugation, disc electrophoresis, gel filtration, immuno-diffusion, fluorescence microscopy, circular dichroism, tissue and organ culture.

Major Findings: 1. A high resolution gel electrophoresis system has been developed utilizing SDS and discontinuous buffers making it possible to solubilize and fractionate all protein and glycoprotein material in a cell membrane.

2. Each membrane system within a cell has its own identifiable protein subunit composition.

3. The surface membranes of cells also have specific subunit compositions but have some identical protein subunits. One-half of the common sized protein subunits in liver and kidney cell surfaces are carbohydrate containing proteins.

4. The insulin receptor for rat liver cell membranes has been identified by binding studies. I^{125} monoiodoinsulin binds to liver membranes with an apparent association constant of 5×10^8 and is displaced with various species of insulin and insulin derivatives in direct proportion to their bioactivity on rat fat pads.

Scientific Significance: 1. The development of a disc stacking system for use with SDS gel electrophoresis has permitted the miniaturization of this technique so that comparisons between the electrical activity of single neuronal cells and their protein subunit composition are now being made (CH BB).

2. Cell surface glycoproteins are implicated in mediating many biological processes such as cell recognition, mitoses, cell versus host destruction of tissue, and cell adhesion. The ability to fractionate membrane glycoproteins and protein and catalogue them by size will allow an understanding of biological processes in chemical terms.

3. The chemical detection of the insulin receptor opens the way to determine the biochemical nature of the defect in diabetes. Important in its own right this disease may provide a model for the understanding of disease processes in which cell behavior is altered by improper functioning of receptor sites or their transducers.

Honors and Awards: None

Publications:

Freychet, P., Roth, J., and Neville, D. M., Jr.: Insulin receptors in the liver: Binding of ^{125}I insulin to the plasma membrane and its relation to insulin bioactivity. Proc. Nat. Acad. Sci. U.S.A., in press.

Freychet, P., Roth, J., and Neville, D. M., Jr.: Monoiodoinsulin: Demonstration of its biological activity and binding to fat cells and liver membranes. Biochem. Biophys. Res. Commun., in press.

Neville, D. M., Jr.: Molecular weight determination of protein dodecyl sulfate complexes by gel electrophoresis in discontinuous buffer systems. Submitted to J. Biol. Chem.

Neville, D. M., Jr. and Glossmann, H.: Plasma membrane protein subunit composition: A comparative study by disc electrophoresis in sodium dodecyl sulfate. Submitted to J. Biol. Chem.

Glossmann, H. and Neville, D. M., Jr.: Glycoproteins of cell surfaces. A comparative study utilizing disc electrophoresis in sodium dodecyl sulfate. Submitted to J. Biol. Chem.

Serial No. M-NC-8
1. Neurochemistry
2.
3. Bethesda, Md.

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Biological and Biochemical Models for the Genetic Disease, Phenylketonuria (PKU)

Previous Serial Number: None

Principal Investigator: Audrey L. Stone

Other Investigators: Seymour Kaufman

Man Years

Total	0.75
Professional	0.50
Other	0.25

Project Description:

Development of a murine model for PKU using X-irradiated sires and a screening test for serum phenylalanine and tyrosine levels as guide for heterozygosity for the phenylalanine hydroxylase gene; investigation of natural history of the enzyme with the use of cell models using murine, human and primate organs.

Objectives: To produce and develop a mutant murine strain with the genetic defect of PKU; to examine organs and cells of human, primate and other species for the expression of phenylalanine hydroxylase activity; to compare in particular the biological and biochemical properties of phenylalanine hydroxylase from human liver and kidney for the possibility of the short-term therapeutic value of kidney cells or tissue transplants in the PKU infant.

Methods: C57 black mice were chosen as standard murine source. Potential sires were X-irradiated at 500 or 600 r total body dose (dose rate 139 r/min). Matings were started at 6 weeks past irradiation with either 8-week old new breeders or 6-month old ex-breeders. Serum phenylalanine and tyrosine were measured by fluorimetric techniques on control mice in groups separated by sex and age differences.

Phenylalanine hydroxylase activity in tissue extracts was determined by radioactive assay developed in this laboratory.

Irradiated sires are producing normal litter sizes after 2-1/2 months.

Major Findings: The range of values of serum phenylalanine and tyrosine for C57 Bl mice 6 weeks and older is the same as that for human controls (although the values are slightly higher). This screening procedure, therefore, mimics that used in the human PKU studies so that the same level of overlap (doubt) may be assumed to be operative in regard to heterozygote detection. The data also show that normal young mice have lower serum values for these amino acids, so that serum-expressed defects in the phenylalanine hydroxylase system must be examined with the appropriate control groups as a function of age. An unusually high serum phenylalanine was found in the Leaden mouse strain, which was selected for this study because of the nature of its pigment mutation.

Phenylalanine hydroxylase levels for livers of the various mouse strains are similar and high. Both rat and mouse kidney show significant levels of the enzyme while human tonsil and mouse cervical node are devoid of measureable activity.

Scientific Significance: A screening program for a murine model for PKU has been shown to be possible. Time and numbers will provide the "mutant" offsprings for testing. Dilute and dilute lethal mutant mouse strains mimic elements in the PKU syndrome. Using the present control data, dispute among other investigators concerning whether or not there is also elevated serum phenylalanine in these strains can be resolved showing elevation in the young mice.

Proposed Course: The screening program for the murine model for PKU will be improved in selectivity by analysis of a single sample for both amino acids on the automatic amino acid analyzer. Primary human and primate cell cultures and fresh autopsy human tissues will be handled in a special biohazard hood enabling biochemical studies on model systems closer phylogenetically to PKU individuals. The genetic search is expected to extend beyond the next fiscal year.

Honors and Awards: None

Publications: None

Serial No. M-NP-GN-47
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The ionic and metabolic basis of neuronal thermosensitivity

Previous Serial Number: Same

Principal Investigators: D. O. Carpenter, J. L. Barker and H. Levitan

Other Investigators: W. S. Snover, R. Seligman, H. Thompson

Cooperating Units: Electroencephalography Branch, NINDS
Behavioral Biology Branch, NICHD

Man Years

Total:	3.7
Professional:	2.6
Other:	1.1

Project Description:

Objectives: This project has been undertaken to investigate the mechanisms which allow nerve cells to respond to changes of temperature and to compare the coding of thermal information in those neurons which mediate thermal sensation with that in those neurons not known to be involved in perception or regulation of temperature.

Methods Employed: Studies on the basic mechanisms of thermosensitivity have been carried out primarily on isolated nervous systems of invertebrates, Aplysia and Navanax. Intracellular recordings were made from single neurons under circumstances where temperature, ionic concentrations of the sea water solution and the metabolic state of the preparation could be controlled and the effects of drugs tested. Experiments on thermosensitivity of mammalian cortical neurons were done by extra- and intracellular recordings of discharges during changes of cerebral temperature (effected by cooling or heating the blood flowing through the carotid rete of the cat).

Major Findings: (1) The role of metabolic processes in determining neuronal thermosensitivity. We have previously shown that an electrogenic sodium pump contributes to membrane potential in Aplysia neurons by the generation of an outward current. Metabolic

inhibitors all produce in these neurons a state of very high conductance, usually with an increase in resting membrane potential as a result of a dramatic increase in the permeability of the membrane to K^+. In contrast, the cardiac glycosides, which are specific inhibitors of the sodium pump, do not cause changes in membrane resistance.

(2) The role of the temperature dependence of passive ionic permeabilities in determining neuronal thermosensitivity. In Aplysia neurons the g_K/g_{Na} ratio is very much lower than in many other preparations, and the temperature dependence of g_{Na} is much greater than that of g_K. This results in a tendency for neurons to be more excitable at higher temperatures, whereas the effect of the activity of the electrogenic Na^+ pump tends to decrease excitability at high temperatures. In the state of poisoning with metabolic inhibitors, however, the potassium conductance is increased so much that the cell is usually silent at all temperatures.

We have also tested the role of these metabolic processes in the mechanism of endogeneous pacemaker activity. In the high conductance state produced by metabolic inhibitors all spontaneous discharge is abolished. Thus the high resistance state appears essential for endogeneous activity. Although endogeneous activity requires the metabolic processes which generate the relative impermeability of the membrane, it does not depend upon activity of the Na^+ pump for it is present when all Na^+ is replaced by Li^+, in absence of external K^+ or in the presence of ouabain.

(3) The ionic mechanisms of the effects of salicylate on nerve cells. Although aspirin is the most commonly used medication, the mechanism of its effects on nerve cells are unknown in regard both to temperature and pain. We have studied the effects of Na^+ salicylate on invertebrate neurons. In both Aplysia and Navanax neurons salicylate has effects on passive ionic permeabilities, especially for K^+ and Cl^-. In both preparations the Cl^- permeability is reduced whereas the K^+ permeability is increased. In most cells in both preparations there is a concomitant hyperpolarization and decreased excitability. In some neurons in Aplysia, however, salicylate causes an increased excitability. Whether there is a different process at work here is presently unknown.

(4) Thermosensitivity of neurons in the cat's motor cortex. As a result of our previous studies documenting the ionic and metabolic basis of thermosensitivity of Aplysia neurons (which are clearly not all specific thermoreceptors) we postulated that these same processes exist in all neurons and result in varying degrees of thermosensitivity. If this is so, then the neurons concerned with processing thermal information need not be any more thermosensitive than those not so concerned, but must be connected in such a way that the thermal information is used.

To test this hypothesis we have studied the thermosensitive properties of large neurons in the cat's motor cortex, an area not known to be involved in temperature regulation. We found that over 50% of these neurons responded in a consistent fashion to changes in temperature. In these neurons, both the percentage of thermosensitive neurons and the degree of average thermosensitivity were greater than others have found for neurons in the hypothalamus (which is known to be involved in thermoregulation). Thus, we conclude that thermosensitivity of a neuron does not necessarily indicate that this information is used by the nervous system.

(5) Collaborative studies with the Department of Physiology, Centro de Investigacion del Instituto Polytechnico Nacional, Mexico City, D. F., Mexico. Dr. Carpenter spent three months in Mexico with Dr. Pablo Rudomin developing with him techniques using the isolated frog spinal cord. The purpose of the project was to develop a preparation in which one could study thermosensitivity of a vertebrate neuron which could be maintained removed from the animal so that one could study effects of ionic changes and drugs. This aim was accomplished and preliminary experiments were made on the temperature dependence of a variety of types of reflexes in the frog cord, particularly the dorsal root reflexes elicited by stimulation of motor or afferent fibers. In addition studies were made and completed on the organization of presynaptic inhibition elicited from afferent, motor antidromic and descending pathways.

Significance to bio-medical research and program of the Institute: (1) A better understanding of the metabolic basis of neuronal function is of considerable importance if we are to ultimately understand the behavior of neurons. It seems clear at this stage in research that much of what maintains neurons as excitable cells is metabolically derived. Thus, manipulation of metabolic processes in nerve cells can change their excitability. The study of simple neuronal systems, as in Aplysia, is a way to extend our present knowledge on the metabolic basis of neuronal function and to provide a basis for exploring similar problems in vertebrates.

(2) In most excitable tissues studied to date, ion diffusion gradients and selective membrane permeability form the basis of neuronal function. The study of how temperature affects these parameters is therefore important as a general property of nerve cells. It is of special interest in Aplysia neurons because of the fact that specific membrane resistance is much greater in this preparation than in many others. As a result, the membrane potential is much more sensitive to the small changes in g_{Na^+} caused by temperature changes. These experiments suggest that the results seen in Aplysia neurons as compared with the classical observations of squid axon may reflect a basic difference between neuronal cell bodies and axons.

(3) We chose to examine the effects of salicylates on molluscan neurons since salicylates are used as antipyretics and analgesics and since no previous research at this level had been reported. Our finding that salicylate decreases both the output from and the effectiveness of input to a neuron, should provide a much needed background for further exploration in vertebrate preparations. We have also found the underlying ionic mechanisms to consist of an increase in the cells' permeability to potassium coupled with a decrease in permeability to chloride. These latter findings are similar to those seen in vertebrate red cell membranes. It is possible that similar mechanisms are involved in salicylate's analgesic and antipyretic effects. These results should also provide a firm beginning for future research on the therapeutic actions of salicylate.

(4) Since we have found a high degree of neuronal thermosensitivity in an area not known to be involved in thermoregulation, we conclude that thermosensitivity is a general property of neurons and that the thermosensitivity of a particular neuron depends on the various temperature-dependent metabolic and ionic mechanisms of the cell. This new insight into neuronal thermosensitivity at the vertebrate level should provide a better background for investigation into vertebrate thermoregulatory processes.

Proposed Course of Project:
The studies on metabolic and ionic basis of membrane potential will be continued and expanded to include direct measurements of Na^+ movements using isotopes. The study on effects of salicylate will also be continued with increasing emphasis on mechanisms in those neurons which are excited by salicylate application. The study of thermosensitivity of cortical neurons has been completed, but the same problem will now be investigated in the isolated frog cord and in other isolated mammalian preparations containing thermosensitive fibers. The collaborative efforts in Mexico will be continued by graduate students there who hopefully will at some point be able to come to this laboratory.

Honors and Awards:
Dr. Carpenter was invited to the Department of Physiology, Centro de Investigacion del Instituto Polytechnico Nacional, Mexico City as a Visiting Professor of Physiology for three months starting January, 1971. He was invited to give a lecture at the Neurophysiology Club meeting at the Atlantic City Federation Meetings, April, 1970. Dr. Carpenter was a Guest Lecturer at the University of Maryland School of Medicine, Department of Physiology, in October, 1970 and at the University of Texas School of Medicine in Galveston, Department of Physiology, in December, 1970.

Dr. Barker was a Guest Lecturer at Yale University, Department of Environmental Physiology in January, 1971.

Publications:

J. L. Barker and D. O. Carpenter, Thermosensitivity of Neurons in the Sensorimotor Cortex of the Cat. Science, 169, 597-598, 1970.

J. L. Barker, H. Levitan and D. O. Carpenter, Effects of Salicylate on Molluscan Neurons. Science (in press).

Serial No. M-NP-GN-48
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The state of ions and water in living cells.

Previous Serial Number: Same

Principal Investigators: M. Hovey, D. O. Carpenter and A. Bak

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	3.0
Professional:	2.1
Other	.9

Project Description:

Objectives: To measure the total concentration of small ions and compare with independent measurements of the concentration of free ions in several types of nervous (Aplysia neurons, squid and lobster giant axons) and non-nervous tissues (barnacle muscle fibers, frog eggs), and simultaneously to determine the ratio of free to immobile water in these tissues.

Methods Employed: The intracellular conductivity of Aplysia neurons and axoplasm is determined with a capacitance-conductance meter consisting principally of an operational amplifier and feedback resistance circuit with a high frequency source. Metal microelectrodes are supported by a micro positioner and electrically connected to the meter. Each electrode is calibrated in normal sea water. By diluting the sea water in finite steps (1 to 100% of normal) a standard calibration curve is drawn and compared with the record taken from the neurons. The intracellular recordings are taken at various temperatures by perfusing the ganglion with sea water flowing through an ice bath.

Major Findings: It is established that the equivalent capacitance measured with platinized metal electrodes at high frequencies (50-300 KHz) varies linearly with the conductivity of normal salt solutions. The equivalent capacitance recorded from the inside of Aplysia neurons is consistently found to com-

pare to 5-10% sea water solutions. The capacitance recorded intracellularly varies little or not at all over a range of temperatures (23° - 11°C). These results suggest that a considerable proportion of intracellular ions and/or water are immobile. In contrast, in squid axon capacitance of axoplasm is similar to that of normal sea water, in agreement with other observations that ions in squid axon are free.

Significance to bio-medical research and program of the Institute: Our results to date suggest that ions in nerve cell bodies exist in a very different state from those in axons. If this be true it is necessary to re-examine many of the concepts which were developed to explain electrical events in axons and which have been assumed to apply to all excitable tissues on the assumption that all ions are free. Moreover, it seems very possible that the state of ions in most cell bodies may be more like that in Aplysia neurons than that in red blood cells and squid axons since the cell bodies contain many more membraneous structures and a higher concentration of organic molecules (which are probably the site of the ion and water binding). Our observations, therefore, may have relevance to all types of cells.

Proposed Course of Project: The technique of equivalent capacitance measurement will be used in other nervous and non-nervous tissues to measure the extent of ion and water binding. In addition, further experiments are planned with Aplysia neurons to measure capacitance over a range of frequencies and under the influence of high Ca^{++} concentration. Aplysia neurons will be analyzed for total Na^{+} and K^{+} content with a helium glow spectrophotometer in order to compare the calculated conductivity with our equivalent capacitance measurements and thus determine the percent of bound ions. To distinguish between bound ions and water, it is proposed to utilize ion specific microelectrodes in Aplysia neurons which will measure the activities of Na^{+} and K^{+} and, in collaboration with Dr. E. Becker, employ the technique of nuclear magnetic resonance to determine the amount of bound water in Aplysia giant neurons. Finally, in collaboration with Dr. Kurt Heinrich of the National Bureau of Standards, single Aplysia neurons will be dissected, freeze dried and analyzed on an ion microprobe to obtain ratios of $Na^{+}:K^{+}:Cl^{-}$, and, if suitable standards can be developed, the absolute concentrations of these ions.

Honors and Awards: None

Publications: D. O. Carpenter, M. Hovey and A. Bak. Intracellular conductance of Aplysia neurons and squid axon as determined by a new technique. Int. J. Neurosci. (in press).

Serial No. M-NP-GN-51
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Serotonin and dopamine as neurotransmitters in the nervous system of Aplysia.

Previous Serial Number: Same

Principal Investigators: D. O. Carpenter

Other Investigators: George Breese, Saul Schanberg and Irwin Kopin

Cooperating Units: Laboratory of Clinical Science, NIMH

Man Years

Total:	0.1
Professional:	0.1
Other:	0

Project Description:

Objectives: To determine the content of serotonin and dopamine in the nervous system of Aplysia and to obtain evidence that they function as neurotransmitters.

Major Findings: Both serotonin and dopamine are present in the nervous system of Aplysia, but are present in different ganglion in very different amounts. Serotonin has been found in heart, peripheral nerves, and all ganglia except the buccal. Dopamine is absent from the heart, some peripheral nerves, and several ganglia but is present in very large quantities in other ganglia and peripheral nerves, as well as some non-neural tissues. The uptake and release of these substances has also been studied.

Significance to bio-medical research and program of the Institute: An understanding of neurotransmitters in a simple preparation aids in the understanding of neurotransmitters in mammals.

Proposed Course of the Project: Project is complete.

Honors and Awards: None

Publications: D. Carpenter, G. Breese, S. Schanberg and I. Kopin. Serotonin and dopamine: Distribution and Accumulation in Aplysia Nervous and Non-Nervous Tissues. Intl. J. Neurosci. (in press).

Serial No. M-NP-GN-63
Laboratory of Neurophysiology

Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: The functional organization of the brain in the initiation and control of voluntary movement

Previous Serial Number: M-CS-P(C)-9

Principal Investigators: Edward V. Evarts, Mahlon DeLong, Nori-ichi Mano

Other Investigators: William T. Burriss, Howard Holbrook

Cooperating Units: None

Man Years: Total: 5.75
Professional: 4.00
Other: 1.75

Project Description:

Objectives: This project is aimed at understanding how the major motor centers of the brain control movement: we are trying to find out how the brain functions when we carry out willed movements. More specifically, we seek to discover what areas of the brain initiate the movement, what areas control and regulate the movement, and how these areas for initiation and control are interrelated.

Methods Employed: Our technique involves the use of microelectrodes to record the activity of individual neurons during natural, voluntary movement in the monkey. This use of the technique of single unit analysis in relation to voluntary movement is analogous to the long-established use of single unit analysis in determining how the brain receives and elaborates its sensory input. The analysis of single cells in relation to afferent input was begun by Adrian a number of decades ago and has now been widely applied in studies of the central nervous system's role in sensation. The technique of single unit analysis has only recently been applied to record the activity of individual neurons in unanesthetized moving animals.

Major Findings:

1. Studies on Extrapyramidal Systems: The Globus Pallidus. There is abundant clinical evidence that the corpus striatum (including the caudate nucleus, the putamen, and the globus pallidus) is an important structure in control of movement, but prior neurophysiological studies in animals have

failed to reveal the way in which cells of these structures participate in movement. The standard techniques of ablation and electrical stimulation in structures such as the globus pallidus and putamen have been rather unrevealing because these structures lie more-or-less halfway between input and output, and the multisynaptic chains between their neurons and motor behavior render an electrical stimulus ineffective: the ease with which electrical stimulus can evoke movement depends upon how close the stimulus site is to the spinal cord motoneuron. Stimulation of the cerebral motor cortex, whose neurons have monosynaptic connections to spinal cord motoneurons, can evoke movement, but stimulation of structures such as globus pallidus are rather ineffective. It was therefore of special value to apply the technique of single unit recording during normal movement to a study of the globus pallidus. The aim here was to observe the activity of neurons during natural movement and find out the way in which such neuronal activity was related to the motor behavior of the animal.

In studies reported in last year's annual report, neurons in the globus pallidus of the monkey had been found to discharge in relation to self-paced movements of the contralateral arm, yet the timing of the discharge in relation to the movements was unclear. The discharge might have been involved in the initiation of movement or might have resulted from sensory feedback. In the present year, an experiment was carried out to determine whether neuronal activity in the basal ganglia precedes or follows the onset of movement. Monkeys were trained to grasp an immovable rod and steadily push or pull, and then to rapidly reverse the direction of the force at the presentation of a visual stimulus. Extracellular recordings were made from neurons in the contralateral putamen and pallidum during repeated sequences of movement. Numerous units in both the putamen and pallidum showed increases or decreases in activity prior to the onset of movement. Related units frequently exhibited different levels of activity during maintained pushing and pulling and in relation to the transient shift between the two steady states. These changes in activity prior to movement indicate that the basal ganglia play a role in the initiation of movement. Since the major efferent projections of the pallidum are to the ventroanterior and ventrolateral nuclei of the thalamus, which in turn project upon the precentral cortex, it would seem that the output from the basal ganglia may influence the activity of the motor cortex prior to the onset of movement.

2. Cerebellar Purkinje Cell Activity. The second general area of work in the laboratory has been carried on by Dr. Nori-ichi Mano, who is supported by a fellowship provided by the Foundations' Fund for Research in Psychiatry. Mano has been working on the activity of single Purkinje cells in the cerebellum in intact monkeys. The results of his experiment on Changes of Simple and Complex Spike Activity of Cerebellar Purkinje Cells with Sleep and Waking, published in Science, have had important theoretical significance for an understanding of the physiology of the Purkinje cell. For these studies, action potentials of cerebellar Purkinje cells were observed in intact monkeys during sleep and waking. Purkinje cells exhibit two sorts of action potentials, called simple and complex spikes, and these two sorts of spikes

were differently affected by sleep. Simple-spike activity (generated by the parallel fiber inputs to the Purkinje cell) was highest during sleep with rapid eye movements as compared with both waking and sleep with electroencephalographic slow waves. In contrast, complex-spike activity (generated by the climbing fiber inputs to the Purkinje cell) was lowest during sleep with rapid eye movements. The complex action potential of the Purkinje cell consists of an initial large spike followed by one or more smaller secondary spikes, and the number of these secondary spikes was found to be independent of the background discharge frequency of the simple spike. This independence suggests a possible role of presynaptic factors rather than the excitability level of the Purkinje cell itself in determining the number of secondary discharges occurring in the complex spike.

Following the completion of this study, Mano continued to investigate Purkinje cell activity, but the new studies involved examination of Purkinje cell in relation to learned movement. Results of these experiments are currently being analyzed, and will be described in next year's annual report.

3. Development of Computer Programs for Analysis of the Cerebral Activity Associated with Learned Movement. In the past the results of the investigations in the laboratory have been analyzed by means of special purpose computers or counters. We have had a variety of special purpose analytic aids in the laboratory, but have never employed a general purpose computer. Within recent years, however, the technical problems associated with data collection have been almost completely overcome, and a major delay in the path of more rapid progress has been data analysis. Thus, it seemed that the time had come for working out systems for having our tape-recorded data analyzed by means of a computer. This has involved setting up computer programs in collaboration with Mr. James Bryan, Chief of the Section on Technical Development. Within the past year these programs have been applied with great success, and our ability to work with large numbers of nerve cells has been greatly expanded.

4. Activity of Postcentral Sensory Cortex Neurons in Association with Movement. The first cerebral region examined to determine the time of occurrence of neuronal discharge in relation to a learned movement was the precentral motor cortex, area 4. Some of the neurons in this area (both pyramidal tract neurons and non-pyramidal tract neurons) were found to discharge as much as 100 msec prior to movement. For these studies on timing, monkeys were rewarded for making a prompt movement in response to a photic stimulus whose time of occurrence was unpredictable. In this situation, reaction times were about 200 msec, and for such reaction times the first activity in motor cortex occurred about 100 msec after the stimulus and 100 msec before the response. For longer reaction times the latency from stimulus to the discharge of units in motor cortex was correspondingly longer, but the interval from motor cortex discharge to movement remained relatively constant: thus, discharge in motor cortex was time-locked to output rather than input. But what of neurons outside motor areas? Is discharge prior to movement restricted to the "motor" division of the sensorimotor cortex, or does such

discharge occur in the postcentral "sensory" division as well? Muscular contraction can be elicited by electrical stimulation of postcentral as well as precentral cortex, and the existence of peripheral sensory inputs to postcentral neurons should not obscure the fact that postcentral neurons receive powerful inputs from non-sensory areas of the brain. To determine the relation between timing of discharge in precentral motor and postcentral sensory cortex, recordings were obtained (in the same monkey) from pre- and postcentral hand areas in association with reaction time performance. The results showed that postcentral activity follows movement initiation (presumably as a result of feedback from the periphery). Thus, recordings in moving animals reveal a striking functional differentiation within the sensorimotor cortex: precentral activity precedes and initiates movement, whereas postcentral activity follows movement and depends on feedback from the periphery.

Significance to Bio-medical Research and the Program of the Institute: The work on the extrapyramidal system is of special interest in relation to mental health research because it seems to lie somewhere between a purely motor structure and a higher level integrating center. Thus, lesions and disturbances of the extrapyramidal system result not only in abnormal movement but also in certain modifications of intellectual and psychic function. Patients with Parkinsonism, for instance, not only have disturbed movements but also show alterations of affect. In addition, there are certain extrapyramidal syndromes associated with mental deficiency (e.g., Huntington's Chorea). It seems clear that an understanding of the way in which the neurons of the extrapyramidal system function will provide important clues as to a number of presently unknown basic mechanisms of mental function.

The work on the cerebellum in the past year has concerned the activity of certain cerebellar nerve cells in association with learned movement. Until recently the work on this project has involved the performance of movements which were thoroughly learned prior to recording. Now we feel it would be important to observe the activity of single nerve cells during the time when a new movement is being learned. Information as to cerebral mechanisms underlying learning is relevant to the problems of mental health research and this is the goal of the work we are now doing on the cerebellum.

Proposed Course of Project: The proposed course of the work of the laboratory will be indicated according to the several areas for which major findings were reported.

1. Studies on Extrapyramidal Systems. This work will continue to be focused on when activity of extrapyramidal neurons occurs in relation to movement. In addition, new areas of the extrapyramidal system will be investigated. One of these is the nucleus subthalamicus, which is a link between the external and internal segments of the globus pallidus. Also, we will study the caudate nucleus.

2. Cerebellar Purkinje Cell Activity. Several current theories propose that one of the inputs to the cerebellar Purkinje cell (the climbing fiber

input) is important in learning. Experimental approaches to testing this hypothesis will be carried out. A guest worker, James Mortimer, will work on this problem.

3. Collaborative Studies with Primate Research Center, Kyoto University. Shortages of positions and travel funds have made it difficult to pursue this collaborative work to the extent that was hoped. Originally we had hoped that Dr. Hiroaki Niki from the Primate Research Center of Kyoto University could come to the NIH to work collaboratively with us. The necessary position was not available, however. Now we have obtained outside funds for Dr. Niki and he will join us in August, 1971 to work on the prefrontal cerebral cortex.

Honors and Awards: None

Publications:

Evarts, E.V.: The motor systems: action upon the environment. In Handler, P. (Ed.): Biology and the Future of Man. New York, Oxford University Press, 1970, pp. 360-367.

Thach, W.T.: Discharge of cerebellar neurons related to two maintained postures and two prompt movements. I. Nuclear cell output. J. Neurophysiol. 33: 527-536, 1970.

Thach, W.T.: Discharge of cerebellar neurons related to two maintained postures and two prompt movements. II. Purkinje cell output and input. J. Neurophysiol. 33: 537-547, 1970.

Mano, N.: Changes of simple and complex spike activity of cerebellar Purkinje cells with sleep and waking. Science 170: 1325-1327, 1970.

Evarts, E.V., Bizzi, E., Burke, R.E., DeLong, M. and Thach, W.T.: Central Control of Movement. Neurosciences Res. Prog. Bull., Cambridge, M.I.T. Press, 1971, vol. 9, 170 pp.

DeLong, M.: Central patterning of movement. In Evarts, E.V. et al.: Central Control of Movement. Neurosciences Res. Prog. Bull., Cambridge, M.I.T. Press, 1971, vol. 9, pp. 10-30.

Bizzi, E. and Evarts, E.V.: Translational mechanisms between input and output. In Evarts, E.V. et al.: Central Control of Movement. Neurosciences Res. Prog. Bull., Cambridge, M.I.T. Press, 1971, vol. 9, pp. 31-59.

Evarts, E.V.: Feedback and corollary discharge: A merging of the concepts. In Evarts, E.V. et al.: Central Control of Movement. Neurosciences Res. Prog. Bull., Cambridge, M.I.T. Press, 1971, vol. 9, pp. 86-112.

Evarts, E.V. and Thach, W.T.: Strategies and tactics in research on central control of movement. In Evarts, E.V. et al.: Central Control of Movement. Neurosciences Res. Prog. Bull., Cambridge, M.I.T. Press, 1971, vol. 9, pp. 113-139.

Serial No. M-NP-GN-64
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Development of electronic instruments pertinent to bio-medical research.

Previous Serial Number: None

Principal Investigators: Anthony Bak

Other Investigators: None

Cooperating Units: Laboratory of Clinical Psychobiology, NIMH,
Office of the Director, Intramural Research, NIMH,
Laboratory of Biophysics, NINDS,
Branch of Surgical Neurology, NINDS and
Laboratory of Neurophysiology, NINDS

Man Years:

Total:	0.5
Professional:	0.5
Other:	0.0

Project Description:

Objectives: To design new tools to improve the methods for recording physiological phenomena.

Methods Employed: With the use of technical literature, using the best possible engineering techniques and selected test instruments, discrete solid state components, micro circuits and micro-components, instruments and systems are designed. The design interface depends on a given project and design prediction.

Major Findings: In collaboration with (1) Dr. Frederick Snyder a micro transmitter power supply has been designed and constructed. The power supply dimensions are 1/4" x 3/8" x 1/10". Micro pre-amplifier/transmitter has been designed using a monolitic die. This will be placed in a flat pack 1/4" x 3/8" x 1/10" with the transmitter.

In collaboration with (2) Dr. Walter Freygang, we have been developing an improved version of a negative feed-back device that accurately reproduces the phase angle of a signal that is separated from our circuit by a very high resistance, such as an

ultra-fine micropipette. This enables one to measure the phase angle of the signal without distortion by the capacity across the walls of the pipette. The device will be used in measurements of the phase angle changes along the length of strands of heart muscle in order to characterize the coupling between the cells.

In collaboration with (3) Drs. Kenneth S. Cole and Choh-Luh Li the equations of Maxwell and Rayleigh for the electrical resistance of suspensions of spheres and cylinders have been widely used to calculate the volume concentration of nonconducting cells in several tissues. The assumptions made in the derivations of these equations are not valid over at least part of the concentration range from 50 to 100% so that such calculations are without analytical basis. Approximations for uniform, uniformly separated, space filling figures and for randomly oriented, uniform and uniformly distributed, conducting planes show that each of the equations is correct for volume concentrations approaching 100%. Analogue measurements were made with conducting paper for circular cylinders in square and hexagonal arrays and with an electrolytic tank for spheres in simple and face centered cubic arrays. The available theories are not entirely satisfactory. Similar measurements were made for a square array of square cylinders and a hexagonal array of hexagonal cylinders and for a cubic array of cubes and a hexagonal array of tetrakaidecahedra. In all cases it was found that the measured volume concentrations agreed with those given by the simple Rayleigh and Maxwell equations, to within the experimental accuracies of about 1%, over all of the concentration ranges measured from 30% or less to 90% or more. These analogue calculations thus provide a basis for the use of the equations over the entire range.

In collaboration with (4) Dr. Choh-Luh Li the analysis of the results of the first series of experiments on normal cortical neurons has been completed. Electrical properties of the cerebral cortical elements were examined by passing current through intracellular micropipette electrodes. It was found that the threshold strength for direct excitation of neurons was $0.20 - 0.40 \times 10^{-9}$ amp. Upon supramaximum strength of stimulation, the neurons discharged at high frequencies up to 500 per second; the frequency of discharges rapidly reduced and in 40 - 110 msec became fairly constant at 45 - 200 per second. The response to direct excitation was followed by hyperpolarization; however, if the excitation was immediately preceded by a prolonged passage of negative current, hyperpolarization tended to be replaced by depolarization and spike discharges. Further, during the period of hyperpolarization the input resistance of the neuron was markedly reduced. Resting membrane potentials of cortical neurons were found to be 59.92 ± 7.45 (SD) mV; of the inexcitable elements, presumably glial cells 70.08 ± 8.62 (SD) mV. Of the neurons, the resistance was 9.17 ± 2.68 (SD) $\times 10^{6}$ ohms; capacitance, 0.69 ± 0.35 (SD) $\times 10^{-9}$ farads; and time constant, 5.69 ± 1.34 (SD) $\times 10^{-3}$ sec. Of the inexcitable

elements, the resistance was in the order of 2.40×10^{6} ohms; capacitance, 1.36×10^{-9} farads; and time constant, 2.83×10^{-3} seconds.

The results of the second series of experiments is subjected to detailed analysis at present and conclusions will be presented in the near future.

In collaboration with (5) Drs. Thomas G. Smith, Jr. and George Murray by employing the voltage clamping amplifier designed by Bak we have been able to obtain 100 millivolt steps within 1 millisecond. This is five to ten times faster than we were able to do using commercially available amplifiers and is fifty to one hundred times faster than other investigators have reported in the literature. Being able to clamp a cell membrane rapidly allows one to measure more accurately the instantaneous or chord conductances, before time-dependent conductances dominate or obscure the measurement. Contrary to previous reports with a slow clamp, we find that steady light decreases the membrane conductance of Limulus photoreceptor cells. The second application of this amplifier has been in the rapid scanning microspectrophotometer Drs. Murray and Smith are developing to measure the visual pigments in photoreceptor cells.

Significance to bio-medical research and program of the Institute: To assist in the recording of physiological phenomena.

Proposed Course of the Project: We plan to continue to develop new physiological instrumentation.

Honors and Awards: None

Publications: K. S. Cole, C. Li and A. F. Bak, Electrical Analogues for Tissues. Experimental Neurology, 24, 459-473 (1969).

C-L. Li, V. M. Okujava and A. F. Bak, Some Electrical Measurements of Cortical Elements and Neuronal Responses to Direct Stimulation with Particular Reference to Input Resistance. Experimental Neurology (in press).

Serial No. M-NP-LI-23
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Neural substrate of mirror display in squirrel monkey (Saimiri sciureus).

Previous Serial Number: Same

Principal Investigators: Paul D. MacLean

Other Investigators: Robert E. Gelhard, George F. Creswell, and John Bartko

Cooperating Units: Theoretical Statistics and Mathematics Section, National Institute of Mental Health

Man Years

Total:	1.9
Professional:	0.6
Other:	1.3

Project Description:

Objectives: This long-term study seeks (1) to identify structures involved in the integration of autonomic and somatic functions in visually guided sociosexual behavior and (2) to obtain information about the cerebral representation of unlearned patterns of behavior. A new series of experiments is attempting to discover the effects of combined destruction of ancient midline fiber tracts of the diencephalon on the innate display behavior of the squirrel monkey. The tracts in question are the fornix, stria medullaris, inferior thalamic peduncle, and mammillothalamic tract. At the same time an analysis is being continued of the effects of lesions of the striatal complex on mirror display.

Methods Employed: The mirror display test for male gothic-type squirrel monkeys has been described in previous project reports (M-NP-LI-17, 1963 and 1964). After a monkey reaches criterion in 30 or more trials it is subjected to bilateral lesions of

the target structures. One type of leucotome devised for the tractotomies is made of spring wire within a number 22 gauge stainless steel tubing. After the tube is introduced to the desired point in the brain by a stereotaxic instrument the spring is extruded a known distance at a right angle and then rotated 360°. Another type of leucotome with a leading edge shaped like a shuffleboard is designed for insertion by the stereotaxic carrier in the horizontal plane.

Major Findings:

Midline tractotomies. In three animals the horizontally directed leucotome failed to section the midline thalamic tracts on both sides. In two cases (B-4 and E-4) the findings were of unusual interest because inadvertent interference with the blood supply resulted in a remarkably symmetrical infarction of the anterior two-thirds of the cingulate gyri. On the first post-operative day both animals were subject to bouts of momentary, intense excitement of a kind never seen in numerous other operated monkeys. Monkey E-4, with the smaller cingulate lesion did not regain the preoperative level of display until the third set of 30 trials three months later. The other monkey (B-4) failed to show interest in the mirror for 40 days. At that time and subsequently, it engaged in a bizarre type of display while standing on all fours.

In a pilot animal (No. 792) the rotating leucotome failed to section the midline thalamic tracts completely on both sides. A second animal (C-4) is still under observation.

Lesions of the globus pallidus. Is there a correlation between the size of pallidal lesions and the decline in incidence of mirror display? Planimetry measurements were made on the brains of five monkeys reported last year in order to calculate the volume of destroyed pallidal tissue. In the single animal (W-3) that regained its preoperative level of performance the volume of destroyed pallidal tissue ranged from one-third to two-thirds of that of the other monkeys. The findings in monkey No.775 indicate that lesions caudally placed have a more drastic effect on mirror display than anterior lesions.

Significance to Biomedical Research and Program of the Institute. The findings in two animals in which accidental interference with the blood supply resulted in symmetrical lesions of the anterior two-thirds of the cingulate gyri provide evidence that these structures exert an influence on innate display behavior of squirrel monkeys. Topographic and volumetric measurements in a series of animals with lesions of the globus

pallidus indicate that both the locus and size of the lesion are critical factors as regards the degree of ensuing deficit in mirror display behavior.

Proposed Course of the Project: To be continued.

Honors and Awards: Items pertaining to Dr. MacLean are as follows:

1) Formal discussant of paper by D. Reis et al, Annual Meeting of the American Neurological Association, 1970.

2) Special Award, American Psychopathological Association, for his scientific contribution to the field of brain function and sexual behavior.

3) Special Award Lecture, "Brain Function and Sexual Behavior," American Psychopathological Association, The Roosevelt Hotel, New York, February 5, 1971.

Publications:

MacLean, P. D.: The limbic brain in relation to the psychoses. In: Black, P. (Ed.): Physiological Correlates of Emotion. New York, Academic Press Inc., 1970, pp. 129-146.

MacLean, P. D.: The triune brain, emotion, and scientific bias. In: Schmitt, F. O. (Ed.): The Neurosciences Second Study Program. New York, The Rockefeller University Press, 1970, pp. 336-349.

MacLean, P. D.: Le cerveau limbique à propos de la tendance paranoide chez l'homme. Confrontations Psychiatriques, 6: 45-64, 1970. (Adapted from "The Paranoid Streak in Man". In: Koestler, A. and Smythies, J. [Eds.]: Beyond Reductionism, London, Hutchinson and Co., Ltd., 1969.)

MacLean, P. D.: Der Paranoide Zug im Menschen. In: Koestler, A. and Smythies, J. (Eds.): Das Neue Menschenbild. Die Revolutionierung der Wissenschaften vom Leben, Vienna, Molden, pp. 254-271, 1970. (Translation of the English edition appearing in 1969).

MacLean, P. D.: Putting on our Thinking Caps, The New York Times, Op.-Ed., January 1, 1971, p. 23.

Sudakov, K., MacLean, P.D., Reeves, A., and Marino, R.: Unit study of exteroceptive inputs to claustrocortex in

awake, sitting, squirrel monkey. Brain Research, (in press).

MacLean, P. D.: The limbic system with respect to self-preservation and preservation of the species. Reprinted in: Masterton, R.B., Fox, R. and Spielberger, C.D. (Eds.): Readings in General Psychology, The Ronald Press, (in press).

MacLean, P. D.: A triune concept of the brain and behavior, Lecture I. Man's reptilian and limbic inheritance; Lecture II. Man's limbic brain and the psychoses; Lecture III. New trends in man's evolution, In: Boag, T. (Ed.): The Hincks Memorial Lectures, (in press).

Serial No. M-NP-LI-39
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Anatomical study of termination of fornix fibers in squirrel monkey.

Previous Serial Number: None

Principal Investigators: Charles E. Poletti and George F. Creswell

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.7
Professional:	0.4
Other:	0.3

Project Description:

Objectives: This project is a neuroanatomical counterpart of the microelectrode study (M-NP-LI-38, 1970) on the mode of action of the hippocampus on structures of the brainstem. It utilizes improved silver staining techniques for demonstrating the termination of fornix fibers in the brainstem.

Methods Employed: In order to section the fornix under direct vision it is necessary to retract the cerebral hemispheres and section the corpus callosum. In three cases described in last year's report parts of the cingulate and frontal cortex were inadvertently damaged. Accordingly, two control animals were prepared in which the corpus callosum alone was sectioned and an attempt was made to duplicate the damage to the cingulate and frontal cortex. An additional animal was prepared in which the fornix was severed on one side and serial sections of the brain were cut in about the same plane as the descending fornix. The Fink and Voneida methods were used for revealing fine degenerating fibers and terminal degeneration.

Major Findings: The findings in the two control brains (FX-5 and FX-6) make it probable that the terminal degeneration previously reported in the nucleus accumbens, lateral septum, preoptic area, anterior hypothalamus, anterior dorsal nucleus of the thalamus, and lateral dorsal nucleus of the thalamus is not the result of destruction of structures other than the fornix. No degeneration could be traced into the perifornical area or the medial forebrain bundle. Section of the corpus callosum, however, probably transects fibers of the fornix longus because a few degenerated fibers were traced bilaterally into the medial septum, the diagonal band of Broca, the preoptic area, the medial portion of the descending fornix, and the mammillary bodies. The lesions of the frontal and cingulate cortex appear to have been responsible for terminal degeneration seen in the caudate nucleus and the ipsilateral anterior medial and anterior ventral nuclei of the thalamus.

The brain sectioned in about the same plane as the descending fornix provided a clear visualization of precommissural fornix fibers which join the medial forebrain bundle and, after splaying out laterally, descend close to the medial border of the optic tract. Some fibers are given off to the tuberal region, but the main stream continues into the posterior hypothalamus. Fibers decussating caudal to the mammillary bodies were traced toward the lateral part of the substantia nigra.

Significance to Biomedical Research and Program of the Institute. This study has demonstrated for the first time in primates the existence of fornix fibers projecting to the tuber cinereum. These fibers which appear to derive from the medial forebrain bundle are not to be confused with the "cornual band of the tuber cinereum" which Cajal described in macrosmatic forms and which descends along the "walls of the medial ventricle." The identification of these fibers is significant in view of the reported suppression of the secretion of ACTH following hippocampal stimulation. The decussating fibers traced laterally into the substantia nigra represents an additional new finding.

Proposed Course of the Project: To be concluded with publication of the results.

Honors and Awards: None

Publications: None

Serial No. M-NP-LI-47
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Unit study of exteroceptive inputs to cingulate cortex of squirrel monkey.

Previous Serial Number: None

Principal Investigators: David S. Bachman and Paul D. MacLean

Other Investigators: None

Cooperating Units: None

Man Years

Total:	1.5
Professional:	0.9
Other:	0.6

Project Description:

Objectives: This study is a continuation of research on extero- and interoceptive inputs to the limbic cortex and deals specifically with the question of somatic, visual, and auditory connections with the cingulate cortex.

Methods Employed: Extracellular unit activity is recorded with platinum microelectrodes in squirrel monkeys prepared with a chronically fixed stereotaxic platform. Visual, auditory, and somatic stimulation is performed in the same manner as described in Project M-NP-LI-34 (1968).

Major Findings: Twenty-one tracks between frontal planes F20 and F5 were explored in 3 monkeys (Nos. 795,797,805), and recordings were obtained from 106 units in the cingulate gyrus and 153 units in the supracingulate cortex. None of the cingulate units responded to auditory or somatic stimulation. The firing rate of one unit was changed by photic stimulation. Eighteen (14%) of 130 supracingulate units tested by somatic stimulation were affected by stimulation of the lower extremities. All but four were activated by light touch. All 18 responded to pressure and to pinprick. The receptive fields were usually large and bilateral.

Significance to Biomedical Research and Program of the Institute. The negative findings suggest that the clinically alleged participation of the cingulate cortex in the appreciation of pain and in the immediate recall of visually presented words does not depend on somatic and visual projections to the cingulate cortex. The negative findings with photic stimulation speak against a transmission of impulses via the nucleus opticus tegmenti and mammillary-thalamic-cingulate system.

Proposed Course of the Project: Concluded with the presentation of the findings at the Federation Proceedings (Abstract: Bachman, D. and MacLean, P.D. Unit study of exteroceptive inputs to cingulate cortex of squirrel monkey. Fed. Proc., 30: 434, 1971) and publication of the results.

Honors and Awards: None

Publications: None

Serial No. M-NP-LI-48
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Unit study of interoceptive inputs to the cingulate cortex of squirrel monkey.

Previous Serial Number: None

Principal Investigators: David S. Bachman and Paul D. MacLean

Other Investigators: None

Cooperating Units: None

Man Years

Total:	1.1
Professional:	0.7
Other:	0.4

Project Description:

Objectives: This study is related to the one described in the preceding project (M-NP-LI-47). It deals with the question of interoceptive inputs to the cingulate cortex. The present work is concerned with the effects of vagal stimulation on cingulate unit activity.

Methods Employed: The experiments to be described depended on developing a successful method for stimulating the vagus nerve in chronically prepared monkeys. In retrospect, it appears that previous attempts had failed because of injury of the nerve by the pull of the electrodes when the monkey turned its neck or was climbing in its cage. Accordingly, a full length body cast was devised which allowed freedom of movement, but prevented turning of the head, while the monkey was in its home cage. This, together with a delicate silastic nerve cuff containing electrodes and miltistranded silver lead-wire, appears to have solved the problem of performing chronic experimentation.

The method of recording unit activity is the same as described in the preceding project (M-NP-LI-47). Vagal stimuli are single or triple shocks of sufficient strength to produce respiratory and/or cardiac changes if administered repetitively.

These effects can usually be obtained with 0.3 msec monophasic constant-current negative pulses at 1-3 ma.

Major Findings: To date four tracks have been explored in 3 monkeys (Nos. 621,623,751). Vagal volleys regularly evoked discharges of the majority of 38 units in the cortex of the middle segment of the cingulate gyrus. Response latencies ranged from 10 to 40 msec. Only two of 20 cells in the supra-cingulate cortex were activated. Fourteen cells examined in the anterior cingulate area were unaffected.

Significance to Biomedical Research and Program of the Institute. Stimulation of the anterior cingulate gyrus is known to elicit autonomic effects, including cardiovascular and respiratory changes. Behavioral studies have implicated the cingulate gyrus in maternal behavior and in hoarding. Clinically, anterior cingulumotomy has been claimed to prevent withdrawal symptoms in individuals addicted to narcotic drugs. There is also some clinical evidence that circuits connected with the cingulate gyrus are involved in the awareness of hunger. The findings of the present study contribute to the knowledge of sensory mechanisms involved in the cortical regulation of visceral functions.

Proposed Course of the Project: To be continued.

Honors and Awards: None

Publications: None

Serial No. M-NP-LI-49
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Exploratory study on actions of biogenic amines in squirrel monkeys.

Previous Serial Number: None

Principal Investigators: Paul D. MacLean, Robert E. Gelhard, and Robert Dorman

Other Investigators: Gian L. Gessa[1] and Jorge Perez-Cruet[1], and Larry Ng[2]

Cooperating Units: 1/ Laboratory of Chemical Pharmacology, National Heart and Lung Institute

2/ Laboratory of Cerebral Metabolism, National Institute of Mental Health

Man Years

Total:	1.3
Professional:	0.5
Other:	0.8

Project Description:

Objectives: This exploratory study seeks information regarding four questions: (1) Will a highly purified form of tryptamine, like the commercial product, produce a state of catatonia in squirrel monkeys similar to that described in Project M-NP-LI-37, 1968? (2) Will 5-hydroxytryptophan produce a similar picture? (3) Will intraventricular 6-hydroxydopamine followed by the systemic administration of L-dopa result in dyskinesia? (4) Will the intraventricular application of norepinephrine or amphetamine affect the monkey's state of alertness and activity?

Methods Employed: A highly purified form of tryptamine was made available by Dr. Donner Denckla of The Roche Institute of Molecular Biology. The other agents were provided by the cooperating units. Animals receiving intraventricular injections were prepared with a chronically fixed stereotaxic platform

which provided both a means of implanting cannulae into the lateral ventricles and of obtaining electroencephalographic recordings. Chemicals were deposited in solid form or injected in solution.

Major Findings:

1. Tryptamine. In three monkeys (Nos. 757,784,790) receiving intraperitoneal doses of purified tryptamine, a drowsy appearance was evident as early as three minutes and catatonia in 9-12 minutes. The pupils were dilated. The smallest dose producing these effects was 80 mg/kg. The picture was similar to that previously described in Project M-NP-LI-37, 1968. There was apparent recovery in 45 to 55 min. The effects of an intraventricular injection of 5 mg of the purified substance were similar, except that "drowsiness" and posturing occurred as early as 1 minute. (Doses of 30 µg - 1 mg were ineffective.) There appeared to be recovery in 35-55 min.

2. 5-Hydroxytryptophan (5-HTP). Nine monkeys (Nos. 742,757, 774,779,782,784,785,787,806) received intraperitoneal injections of 5-HTP in doses ranging from 30-65 mg/kg. Symptoms developed more slowly than with tryptamine. An apparent state of drowsiness appeared within 5 to 30 min., and akinesia with posturing developed within 10 to 30 min. Animals receiving the larger doses became cataleptic, with increased muscle tone being demonstrable by the electromyogram. The manifestations would persist as long as five hours. In one animal (No.785) receiving a prior course of treatment with parachlorophenylalamine followed by pargyline, the catalepsy induced by 5-HTP persisted for more than six hours. Pretreatment with RO-4-4602 (50 mg) prevented catalepsy in two monkeys (Nos. 742 and 806). Methysergide (3 mg) had no counteractive effect (No. 787). The EEG recorded from the outer convexity of the brain was characterized by the disappearance of alpha and beta activity. In one monkey (No. 774) with a spike focus in the hippocampus associated with tissue damage at the electrode site, 5-HTP precipitated hippocampal seizures.

3. 6-Hydroxydopamine (6-OHDA). Findings reported on the rat suggest that 6-OHDA may damage neurons containing norepinephrine and dopamine. If so, the corpus striatum should be among the structures most severely damaged. Because of this Section's interest in striatal functions it was significant to learn whether or not intraventricular 6-OHDA would produce persisting changes of behavior in squirrel monkeys. In four treated animals (Nos. 743,790,793,815) transient circling, pareses, and convulsive-like symptoms were sometimes observed, but no enduring

behavioral changes. When these same animals were challenged by intraperitoneal doses of L-dopa (25 mg) and MK 485 (2.5 mg), the manifestations included hyperactivity, scratching, incoordination, choreiform movements, and hemiballismus. Two of these animals (Nos. 793, 815) following 1 mg of apomorphine developed curious athetoid movements of the upper and lower extremities, instability, and hyperactivity. Later they pushed against the top of the cage in a kind of obstinate progression. In two control monkeys (Nos. 789, 811) L-dopa alone or apomorphine alone produced similar, but less pronounced, symptoms.

4. Intraventricular norepinephrine. Two animals (Nos. 743 and 790) received a ventricular injection of norepinephrine in doses ranging from 50 µg to 1 mg. The animals appeared as though under mild sedation. Intraventricular amphetamine in a dose of 100 µg or 1 mg was without definite effect.

Significance to Biomedical Research and Program of the Institute.

1) It has been reported that in schizophrenic patients exacerbation of symptoms may be associated with a rise in urinary tryptamine. It is known that tryptamine may be metabolized into dimethyltryptamine, a psychotogenic substance. The present studies contribute to the knowledge of the action of two naturally occurring amines, tryptamine and 5-hydroxytryptophan.

2) Dyskinesias are among the untoward effects of L-dopa in the treatment of Parkinson's disease. The experiments reported here on 6-hydroxydopamine in conjunction with L-dopa (or apomorphine) demonstrate that dyskinesias can be produced experimentally in the monkey.

3) The sedative-like effects of intraventricular norepinephrine in the squirrel monkey are in agreement with findings in other species, and would seem not to be in accord with the clinical theory that mania is due to an excess of cerebral norepinephrine.

Proposed Course of the Project: To be concluded with the publication of a short communication.

Honors and Awards: None

Publications: None

Serial No. M-NP-LI-50
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Neural substrate of olfactory detection and discrimination in the rat.

Previous Serial Number: None

Principal Investigators: Burton Slotnick

Other Investigators: Robert Gelhard

Cooperating Units: None

Man Years

Total:	1.3
Professional:	0.8
Other:	0.5

Project Description:

Objectives: Inadequate techniques for presenting olfactory cues have been a major deterrent to the study of the role of olfaction in the behavior of animals. The present study is employing an improved olfactometer for use with small animals for investigating neural structures involved in the detection and the discrimination of odors. A next step will be the investigation of the incentive value of a variety of natural odors and pheromones.

Methods Employed: The apparatus consists of an odorizer leading to an air-flow test chamber. The odorizer has a variable pressure air pump which forces air through a series of particle filters and drying and deodorizing elements. Through the use of independent air channels the deodorized air is saturated with an odorant and exhausted through electrically operated 3-way valves delivering a known amount of odorant to the test chamber. Stimulus intensity may be varied by changing the rate of airflow or by dilution of the odorant. The test chamber consists of a glass tunnel equipped with stainless steel response keys and a water delivery mechanism. With the use of standard operant

techniques, rats are trained to detect or discriminate odor stimuli for water reinforcement. Air entering the chamber is continuously exhausted. For detection experiments the animal is trained to face an incoming fresh air stream and respond whenever it detects an odor. In discrimination training one of two odors is presented in random order. Only responses to one of the odors are reinforced. As a check on postoperative capability of performance the rats are also trained in a brightness discrimination.

Major Findings: Experiments thus far have focused on obtaining essential background information regarding the detection of odors before and after bilateral bulbectomy. A dilution of 10^{-5} amyl acetate in water was used in training four animals. All four showed reliable detection responses at a dilution of 10^{-7} but not at 10^{-8}. In two of these animals subjected to unilateral bulbectomy there was an approximate tenfold increase in detection thresholds, but no deficit at suprathreshold intensities. Two animals subjected to bilateral removal of the olfactory bulbs showed complete retention of the brightness discrimination problem, but were unable to detect the training odor.

Two other rats were bilaterally bulbectomized prior to training. Both showed normal acquisition of the brightness discrimination problem but no evidence of odor detection after extensive training at high stimulus intensities. The next step will be to test the effects of lesions of tertiary olfactory structures.

Significance to Biomedical Research and Program of the Institute. The type of olfactometer used in these experiments will help to remove a large void in the knowledge of behavior of macrosmatic animals. It eliminates most of the difficulties encountered in earlier studies of olfactory perception in which "still air" presentation of odors was employed. It also has several advantages over other types of currently used air-flow tunnels, including a provision for evaluating both detection and discrimination functions and a comparison of an animal's performance in response to olfactory and non-olfactory cues.

Proposed Course of the Project: To be continued.

Honors and Awards: Items pertaining to Dr. Slotnick are as follows:

1) Invited Lecture: "Some Experiments on Neural Control of Maternal Behavior". American Museum of Natural

History, New York, New York, April 1, 1971.

2) Invited Lecture: "Species-Dependent Effects of Brain Lesions on Behavior". Hunter College, New York, New York, April 2, 1971.

Publications: None

Serial No. M-NP-LI-51
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Olfactory versus non-olfactory cues in acquisition of learning sets.

Previous Serial Number: None

Principal Investigators: Barry Nigrosh and Burton Slotnick

Other Investigators: None

Cooperating Units: None

Man Years

Total:	1.0
Professional:	0.7
Other:	0.3

Project Description:

Objectives: The purpose of this study is to compare the ability of rats to acquire a reversal learning set when olfactory and auditory discriminative cues are used. A reversal learning set describes an increase in learning speed over a series of discrimination problems in which the positive and negative stimuli are alternately reversed after each problem in the series is learned.

Methods Employed: The training methods and apparatus were the same as those described in the preceding project (M-NP-LI-50). Eight animals were initially trained to discriminate between a flashing and a steady light. They were then divided into two groups, matched on the basis of acquisition performance. One group was given further training on discrimination between two odors and the other on discrimination between two tones until a criterion performance was achieved. Following acquisition, the positive and negative stimuli were reversed and testing resumed until criterion was reached. Such reversals were repeated until there was no further improvement in the subject's performance.

Major Findings: During the initial acquisition the "odor" group performed significantly better than the "tone" group. In the first reversal task, the "odor" group showed significant savings in learning while the "tone" group took significantly longer to learn the new problem. During subsequent reversals the "odor" group showed a rapid increase in learning speed with successive reversal problems, and by the fifth reversal most animals were making only a few errors prior to achieving criterion. By the fifth reversal animals in the "tone" group showed little improvement.

Significance to Biomedical Research and Program of the Institute. The results of this experiment demonstrate that the rat makes better use of olfactory than auditory information in solving a specific problem and that a reversal learning set is acquired much more readily when odor cues are employed. The findings call for a reevaluation of generalizations about problem-solving abilities of rats that have been based on experiments using non-olfactory cues.

Proposed Course of the Project: Concluded

Honors and Awards: None

Publications: None

Serial No. M-NP-MP-3
1. Laboratory of Neurophysiology
2. Membrane Physiology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Electrical, ionic and physical properties of muscle.

Previous Serial Number: Same

Principal Investigators: S. I. Rapoport

Other Investigators: J. Bidinger, R. Fitzhugh

Cooperating Units: Section on Technical Development
National Institute of Mental Health (Mr. James Bryan)

Laboratory of Biophysics
National Institute of Neurological Diseases and Stroke

Man Years
Total: 2.4
Professional: 0.9
Other: 1.5

Project Description

Objectives: (a) To determine the elastic and plastic properties of the muscle fiber membrane (sarcolemma) and relate them to the physiological function of the fiber under conditions of tension.

(b) To determine the factors controlling the size and electrical characteristics of the transverse tubular system (T system) in muscle fibers and to relate properties of the transverse tubular system to excitation-contraction coupling and the electrical properties of the muscle fiber.

Methods Employed: (a) Photomicrographic techniques are used to study a single fiber under high magnification. The fiber is held by a transducer tension device, and measurements are made with usual amplification and recording techniques. Micromanipulation of the fiber is performed. Various mathematical techniques are used and analysis of data is made with the use of a computer. In addition, regions on the fiber are sucked into a pipette with controlled pressure. Theoretical models for elasticity of parts of the fiber are formulated and tested by analytical procedures.

(b) Extracellular action currents and twitch tensions of a single muscle fiber are recorded with usual techniques. Measurements are made as a function of extension in different bathing solutions. Data are analyzed in terms of the theory of the velocity of the action potential, using the relation of the transverse tubular system to action potential and contraction properties of muscle.

Major Findings: (a) The sarcolemmal tubular preparation of frog muscle was studied as a function of tension and extension. From the increase in length and change in curvature of the tube the longitudinal and circumferential elastic moduli, E_l and E_c, as well as Poisson's ratio μ, could be evaluated by means of a model developed. The model was found to apply to the preparation only in the range of reversible extensions. It was found that at zero tension $E_l = 3.3 \times 10^7$ dyne/cm^2, and $E_c \simeq 0.345 \times 10^7$ dyne/cm^2, assuming a sarcolemmal thickness of 0.1 μ. The ratio E_l/E_c for the range of extensions studied was 7.8, which indicates that the sarcolemmal tube is much less extensible in the longitudinal direction. Poisson's ratio was 0.2. The results were independent of whether the tube was formed at whole fiber rest length or at a fiber extension of 40%. Since the initial elongation of the sarcolemmal tube at zero tension, as compared to its length in the whole fiber at zero tension, was 26%, the sarcolemma probably does not contribute to resting fiber tensions for sarcomere lengths < 3.0 μ. The elastic properties of the whole fiber were also evaluated, and at zero tension E (fiber) was calculated to be 1.9×10^5 dyne/cm^2. This work has been published as an abstract: Rapoport, S.I. and Fitzhugh, R.: Anisotropic elastic properties of frog muscle sarcolemma in the region of reversible extension, 15th Annual Meeting, Biophysical Society, Feb. 15, 1971, New Orleans, La., p. 200a.

The elastimeter method was used on the surface of a single muscle fiber of the frog semi-tendinosus as a means to obtain the relative contributions of sarcolemma and myoplasm to resting fiber tension at different extensions. A bleb was sucked into a flat mouthed pipette and its vertical displacement was measured with increasing and then decreasing suction pressures. At higher pressures an external membrane, probably the outer layers of the sarcolemma, separated from the inner myoplasmic region, and the hysteresis of the displacement-pressure curve permitted calculation of the elastic tension of this part of the sarcolemma as a function of sarcomere length. Calculations based on elastimeter observations showed that the sarcolemma did not contribute to intact fiber tension at sarcomere lengths below 3 μ, that it contributed about 10% or less between 3 and 3.75 μ, and more so with further extension. The sarcolemmal elastic modulus was 5×10^6 dyne/cm^2, (assuming a thickness of 0.1 μ) at sarcomere lengths between 3 and 4 μ, and increased with further extension. By means of a model, the myoplasmic elastic modulus was calculated from elastimeter observations and was used to obtain a myoplasmic length-tension curve, for sarcomere lengths $\leq$ 3.5 μ, which agreed with intact fiber observations.

(b) Single muscle fibers of the semi-tendinosus of Rana Pipiens were stretched at room temperature. The twitch force relative to the force at L_o, F/F_o , and the velocity of the action poten-

tial θ, calculated from action currents at two external electrodes, were measured. For stretches > 40%, $\theta/\theta_o = 1.13 \pm 0.02$ S.E. ($P<.05$). The transverse tubular system was disrupted by placing a fiber in 3-400 mm glycerol-Ringer for one hour. Both θ/θ_o and F/F_o decreased initially and then returned to approximate base line in one hour. When the fiber was returned to Ringer, $F/F_o = 0$ usually within a few minutes. θ/θ_o increased maximally by 90 ± 9 S.E. % within a few minutes and then declined until conduction failed after about 15 minutes. In two of 17 fibers in which $F/F_o = 0$, conduction did not fail and θ/θ_o became constant with time. The fibers were then stretched by 60 and 90% without a significant increase in velocity. A third fiber, treated with 200 mM glycerol-Ringer in which $F/F_o < 5\%$, was stretched by 40% without affecting θ/θ_o. Thus, disruption of the T system by glycerol did not produce a decrease in velocity with stretch, which might have occurred if the T system were a source of unfolded membrane. This work has been published as an abstract: S.I.Rapoport: Velocity of action potential of frog muscle as a function of stretch and glycerol treatment, Annual Meeting, Society General Physiologists, Sept. 5-8, 1970, Woods Hole, Mass.

Significance: (a) A knowledge of the mechanical properties of the sarcolemma and myofibrils, and of their relative contribution to tension as a function of stretch, is required to understand the process of contraction and of the resistance of the muscle to stretch under physiological conditions. Correlation between electromicroscopic structure of the sarcolemma and myofibrils and their properties permits a better understanding of the molecular forces regulating tension.

(b) The transverse tubular system is thought to be the pathway for the flow of current between the inside and outside of the muscle fiber, and thus necessary for the coupling between the electrical events at the surface of the cell and the mechanical events within the cell. In order to explain the coupling in detail, it is necessary to know the electrical and physical properties of the tubules. This project is a continuation of a previous study which proposed that the transverse tubular system contains fixed charges which participate in the regulation of excitation-contraction coupling.

Proposed Course: (a) To analyze the data on tension in terms of several models which have been formulated, and to make accurate estimates of the contribution of sarcolemma and myoplasm to fiber tension.

(b) To analyse the data in terms of current models of the transverse tubular system.

Honors and Awards: None

Publications: Rapoport, S. I.: Mechanical properties of the sarcolemma and myofibrils in frog muscle as a function of sarcomere length. J. Gen. Physiol. (in press).

Serial No. M-NP-MP-8
1. Laboratory of Neurophysiology
2. Membrane Physiology
3. Bethesda, Maryland

PHS-HSMHA-NIMH
Individual Project Report
July 1, 1970 through June 30, 1971

Project Title: Transport Mechanisms Across Membranes

Previous Serial Number: Same

Principal Investigators: S. I. Rapoport

Other Investigators: C. F. Patlak, J. Bidinger, H. Thompson, L. I. Mann, I. Klatzo, M. Hori

Cooperating Units: (a) Theoretical Statistics and Mathematics Section, National Institute of Mental Health
(b) Behavioral Biology Branch, National Institute of Child Health and Human Development, N.I.H.
(c) Laboratory of Neuropathology and Neuroanatomical Sciences, National Institute of Neurological Diseases and Stroke, N.I.H.

Man Years
Total: 2.9
Professional: 1.4
Other: 1.5

Project Description:

Objectives: To consider and amplify the theory of transport of substances across artificial and cellular membranes, and to relate transport to membrane potential and function.

Methods Employed: A variety of mathematical techniques are used in conjunction with the theory of transport and its coupling to metabolism, within the formalism of irreversible thermodynamics. Theoretical considerations are derived from principles of physical chemistry and biochemistry, and from experimental observations on neuronal and other cellular membranes.

For the blood brain barrier project (b), high impedance pH and d.c. recording methods were used on the cortex of the anesthetized cat. Surgical procedures for opening the skull and dura were also used. Photographic and histological procedures were also used on the brain of the rabbit.

Major Findings:
(a) A model of the Na-K exchange pump was elaborated. The Na-K exchange pump is represented as a net stoichiometrically coupled reaction, r, involving ATP, Na^+ and K^+, and is located in the active region of the cell membrane. The reaction rate is $J_r = L_{rr}(-\Delta F_r)$, where ΔF_r is the free energy change of the reaction. ΔF_r includes membrane potential ϕ_2 in the absence of 1:1 coupling between Na^+ and K^+, and the reaction rate is potential dependent under these conditions. At the same time the pump will produce a potential H which is the difference between membrane potential and the diffusion potential as calculated with constant field assumptions. In the absence of 1:1 coupling, the pump is electrogenic. The feedback relation between reaction rate and membrane potential makes the membrane resistance in the presence of the pump less than or equal to the resistance in its absence, at the same membrane potential. H depends on stoichiometry, reaction rate, and passive ionic conductances. Experimental verification of the model depends on the accuracy of permeability determinations. Dissipation and efficiency of transport can be calculated also.

Experimental verification of the model of the Na-K exchange pump was made on the Na^+ loaded frog sartorius muscle. These muscles were depleted of K^+ and loaded with Na^+ in a K^+ -free soaking in solutions by Cross, Keynes and Rybova (J. Physiol. 181, 865, 1965). By use of the model, their potentials and fluxes were analyzed after they were returned to warm Ringer containing 10 mm K^+, when they actively extruded Na^+ and accumulated K^+ to approach normality. The following parameters were calculated: hyperpolarization due to the pump, passive flux, net flux, active flux, reaction rate, stoichiometric ratio of K^+ to Na^+, free energy change of the net reaction, reaction conductance L_{rr}, effect of active transport on membrane resistance, and efficiency and dissipation of transport. The model was found to apply to muscles which were considered normal but not to muscles that had been soaked in Ca^{++} -free soaking-in solutions. Calculations demonstrated that an active K^+ influx was coupled to an active Na^+ efflux. Hyperpolarization was ascribed to pump activity and not to extracellular K^+ depletion. The rate of ATP hydrolysis, calculated from the data by means of the model, agreed with the rate obtained by more direct measurements. The calculated conductance coefficient L_{rr} also agreed with the value obtained from the relation of Na^+ tracer efflux to external K^+.

(b) Osmotic breakdown of the blood brain barrier. pH and d.c. potential measurements had been made on the parietal cortex of the anesthetized cat under artificial ventilation (cf. Rapoport, J. Physiol., 170, 238-49, 1964). Following an intravenous injection of $NaHCO_3$, the surface of the cortex becomes transiently acidic, and this response was proposed to be indicative of the blood brain barrier to HCO_3^-. It was found to be

affected by the nature and osmolality of topically applied solutions. In decreasing order of effectiveness with respect to solution osmolality, $NaNO_3$ > NaCl > urea > ethanol in reducing the response in a graded manner. Effectiveness was related to the reduction of the peak acidic response and to the increase in long term alkalinization. A model for blood brain barrier breakdown was proposed, which could explain the above results. The concentrated solutions were hypothesized to shrink cells at the barrier by virtue of their effective osmotic pressure, which is defined as the product of the solution osmotic pressure $RT\sum_i C_i$ (where R is the gas constant, T absolute temperature, and C_i concentration of osmotically effective solutes) and of the reflection coefficient, σ_i. It was found that for the four substances tested, $\sigma_{NaNO3} > \sigma_{NaCl} \geq \sigma_{urea} > \sigma_{ethanol}$. (the closer the reflection coefficient is to 1, the more effective is the shrinkage of the cells). This order of effect or of reflection coefficients is the same order as was found by Overton (Viertel. Naturforsch. Ges. in Zurich, 40: 159, 1895) in his study of the effect of osmotic agents on plant cell shrinkage , and supports the blood brain barrier model.

The following work was done in collaboration with Drs. Hori and Klatzo. In the rabbit, Evans blue dye was injected intravenously and the cortical surface exposed. Different osmotic concentrations of a test substance dissolved in distilled water were applied to different cortical regions to find the threshold for barrier opening, which was defined as the lowest osmolality which produced a blue staining outside of the pial vessels. Reversibility of opening was also studied by injecting Evans blue 1/2 hour following damage to the barrier. Thirteen solutes were studied. The molecular weights of the non-electrolytes were less than 100, so as to minimize diffusion differences between them, and three different electrolytes were studied. It was found that the barrier to dye was opened reversibly by the electrolytes and lipid insoluble non-electrolytes, but the more lipid soluble non-electrolytes broke down the barrier irreversibly. These observations suggested that the electrolytes and lipid insoluble non-electrolytes damaged the blood brain barrier osmotically, perhaps by shrinking endothelial cells of the brain vasculature and opening up the tight junctions between them. The lipid soluble non-electrolytes may have destroyed the membranes of these cells.

(c) Passive and active transport among fetal compartments of the sheep. An analysis was performed, in collaboration with Dr. Mann, of the changes in compartment volumes and ionic concentrations in the sheep fetus as a function of duration of gestation.

A model for intercompartmental transport was proposed on the basis of experimental data. At day 50, there is a net efflux of K^+, Na^+ and water from the allantoic compartment and a net influx into the amniotic compartment. At day 105 ionic and water fluxes are reversed in each compartment. Na^+ is probably transported actively out of the allantoic compartment at day 50, and K^+ may be transported actively into the allantoic compartment at day 105.

(d) Theoretical analysis of net tracer flux due to volume circulation in a membrane with pores of different sizes. Relation to solute drag model. This work has been done in collaboration with Dr. Patlak. When an osmotic pressure across an artificial membrane, produced by a permeable electrical neutral solute on one side of it, is balanced by an external pressure difference so that there is no net volume flow across the membrane, it has been found that there will be a net flux of a second electrically neutral tracer solute, present at equal concentrations on either side of the membrane, in the direction that the "osmotic" solute diffuses. This has been ascribed previously to solute interaction or drag between the tracer and the osmotic solutes. An alternative model is proposed which considers the membrane to have pores of different sizes. Under general assumptions, this "heteroporous" model will account for both the direction of net tracer flux and the observed linear dependence of unidirectional tracer fluxes on the concentration of the osmotic solute. The expressions for the fluxes of solutes and solvent are mathematically identical under the two models, but an inequality is derived which must be valid if the heteroporous one is correct. The application of this inequality indicates that the heteroporous model can account for most of the published observations. When dextran is the osmotic solute, the solute interaction model appears more likely.

Significance to bio-medical research and the program of the Institute: (a) The functioning of excitable tissue (nerve, muscle) depends on the maintenance of the resting potential by active mechanisms which require energy and may extrude Na^+ and accumulate K^+. The theory relates, for the first time, metabolic rate and stoichiometry of the active transport reaction to the neurophysiological parameters of membrane potential, hyperpolarization, membrane resistance and ionic currents. Data which previously were incompletely interpreted on the electrogenic pump in muscle were shown to fit into the model. The model should therefore be applicable to a variety of nervous and muscle tissues and proposes for the first time feedback relations between metabolic activity and nervous function. (b) The model for blood brain barrier breakdown is new. It proposes that the barrier can be broken down irreversibly, as it has in the past, or reversibly, by shrinkage of possible endothelium cells, because of osmotic action. The reversible breakdown of the barrier

could be of significance to the treatment of cerebral diseases by facilitating drug passage, as well as to the treatment and understanding of cerebral edema. (c) The model and analysis of fetal transport are important to the understanding of general transport mechanisms as well as the fetal-maternal relation during gestation. (d) The circulation model for active flux clarifies one of the problems in interpreting the phenomenological coefficients in biological and artificial membranes. The solute-solute interaction model had been proposed for active transport in biological membranes such as toad skin, and in view of the new interpretation, it is hoped that the biological data can be reevaluated.

Proposed course of project: (a) The theory of the Na-K exchange pump will be applied to muscle and other excitable tissue in an effort to interpret biological data as well as to test its applicability. (b) Further evidence for demonstrating that osmotic agents shrink barrier cells will be looked for.

Honors and Awards: None

Publications:

Rapoport, S. I. The effect of concentrated solutions on the blood brain barrier. American J. Physiology. 219, 270-274, 1969.

Rapoport, S. I. and L. I. Mann. Analysis of transport in the compartments of the sheep fetus. Biol. Neonat. 16, 313-322, 1970.

Patlak, C. S. and S. I. Rapoport. Theoretical analysis of net tracer flux due to volume circulation in a membrane with pores of different sizes. Relation to solute drag model. J. General Physiology. 57, 113-124, 1971.

Rapoport, S. I. The cortical acidic response to intravenous $NaHCO_3$ and the nature of the blood brain barrier. International J. Neurosciences. (in press).

Rapoport, S. I. The Na-K exchange pump. Part II. Analysis of Na^+ loaded frog sartorius. Biophysical J. (in press).

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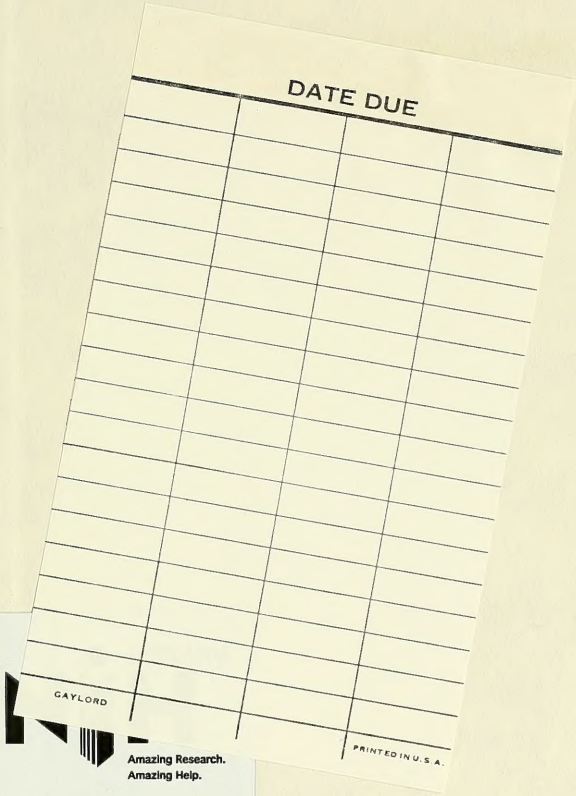

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